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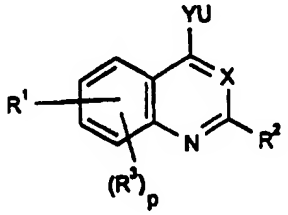
(54) Title: FUSED HETEROCYCLIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS

(57) Abstract

Substituted heteroaromatic compounds of formula (I) and in particular substituted quinolines and quinazolines, are protein tyrosine kinase inhibitors. The compounds are described as are methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of cancer and psoriasis, or a salt or solvate thereof; wherein X is N or CH; Y is a group $W(CH_2)$, $(CH_2)W$, or W, in which W is O, $S(O)_m$ wherein m is 0, 1 or 2, or NR^a wherein R^a is hydrogen or a C_{1-8} alkyl group; R^1 represents a phenyl group or a 5- or 6-membered heterocyclic ring containing 1 to 4 heteroatoms selected from N, O or $S(O)_m$, wherein m is as defined above, with the provisos that the ring does not contain two adjacent O or $S(O)_m$ atoms and that where the ring contains only N as heteroatom(s) the ring is C-linked to the quinazoline or quinoline ring, R^1 being optionally substituted by one or more R^3 groups; P = 0 to 3; U, R^2, R^3 are as defined in the application.



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FUSED HETEROCYCLIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS

The present invention relates to a series of substituted heteroaromatic compounds, methods for their preparation, pharmaceutical compositions containing them and their use in medicine. In particular, the invention relates to quinoline and quinazoline derivatives which exhibit protein tyrosine kinase inhibition.

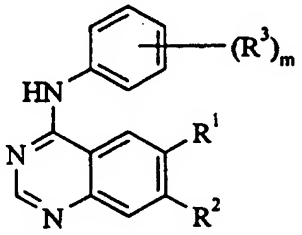
Protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl resldues in various proteins involved in the regulation of cell growth and differentiation (A.F. Wilks, Progress in Growth Factor Research, 1990, 2, 97-111; S.A. Courtneidge, Dev. Supp.l, 1993, 57-64; J.A. Cooper, Semin. Cell Biol., 1994, 5(6), 377-387; R.F. Paulson, Semin. Immunol., 1995, 7(4), 267-277; A.C. Chan, Curr. Opin. Immunol., 1996, 8(3), 394-401). Protein tyrosine kinases can be broadly classified as receptor (e.g. EGFr, c-erbB-2, c-met, tie-2, PDGFr, FGFr) or non-receptor (e.g. c-src, lck, Zap70) kinases. Inappropriate or uncontrolled activation of many of these kinase, i.e. aberrant protein tyrosine kinase activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth.

Aberrant activity of protein tyrosine kinases, such as c-erbB-2, c-src, c-met, EGFr and PDGFr have been implicated in human malignancies. Elevated EGFr activity has, for example, been implicated in non-small cell lung, bladder and head and neck cancers, and increased c-erbB-2 activity in breast, ovarian, gastric and pancreatic cancers. Inhibition of protein tyrosine kinases should therefore provide a treatment for tumours such as those outlined above.

Aberrant protein tyrosine kinase activity has also been implicated in a variety of other disorders: psoriasis, (Dvir et al, J.Cell.Biol; 1991, 113, 857-865), fibrosis, atherosclerosis, restenosis, (Buchdunger et al, Proc.Natl.Acad.Sci. USA; 1991, 92, 2258-2262), auto-immune disease, allergy, asthma, transplantation rejection (Klausner and Samelson, Cell; 1991, 64, 875-878), inflammation (Berkois, Blood; 1992, 79(9), 2446-2454), thrombosis (Salari et al, FEBS; 1990, 263(1), 104-108) and nervous system diseases (Ohmichi et al, Biochemistry, 1992, 31, 4034-4039). Inhibitors of the specific protein tyrosine kinases involved in these diseases eg PDGF-R in restenosis and EGF-R in psoriasis, should lead to novel therapies for such disorders. P56lck and zap 70 are indicated in disease conditions in which T

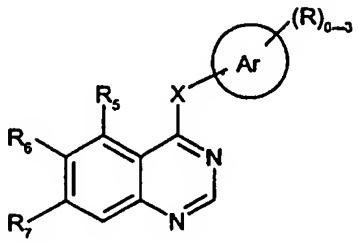
cells are hyperactive e.g. rheumatoid arthritis, autoimmune disease, allergy, asthma and graft rejection. The process of angiogenesis has been associated with a number of disease states (e.g. tumourogenesis, psoriasis, rheumatoid arthritis) and this has been shown to be controlled through the action of a number of receptor tyrosine kinases (L.K. Shawver, DDT, 1997, 2(2), 50-63).

EP0635507 discloses a class of tricyclic quinazoline derivatives of the formula:



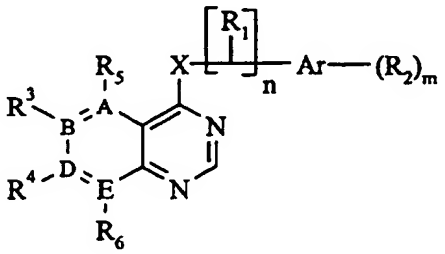
wherein R^1 and R^2 together form specified optionally substituted groups containing at least one heteroatom so as to form a 5 or 6-membered ring, in which there is a N atom at the 6 position of the quinazoline ring; R^3 includes independently hydrogen, hydroxy, halogeno, (1-4C)alkyl, (1-4C) alkoxy di-[(1-4C)alkyl]amino, or (2-4C)alkanoylamino. The above citation notes that receptor tyrosine kinases in general, which are important in the transmission of biochemical signals initiating cell replication, are frequently present at increased levels or with higher activities in common human cancers such as breast cancer (Sainsbury et al, Brit. J. Cancer, 1988, 58, 458). It is suggested that inhibitors of receptor tyrosine kinase should be of value as inhibitors of the growth of mammalian cancer cells (Yaish *et al.* Science, 1988, 242, 933). This citation therefore has the aim of providing quinazoline derivatives which inhibit receptor tyrosine kinases involved in controlling the tumourigenic phenotype.

WO 95/15758 discloses aryl and heteroaryl quinazoline derivatives of formula



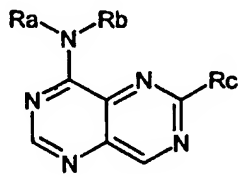
wherein X includes a bond, O, S, SO, SO_2, C≡C, C=C, CH_2 and NH; Ar includes phenyl, naphthyl, naphthalenyl, indolyl, pyridyl, piperidinyl, piperazinyl, dihydroquinolinyl, tetrahydroquinolinyl, thienyl, indanyl, pyrazolyl and 1,4-benzodioxanyl; and R_5, R_6 and R_7 independently include hydrogen, alkyl, alkylthio, cycloalkyl, hydroxy, alkoxy, aralkoxy, aryl, halo, haloalkyl, carboxy or carbalkoxy; as inhibitors of CSF-1R and/or p56lck receptor tyrosine kinase activity.

WO 95/19774 discloses bicyclic derivatives of formula:



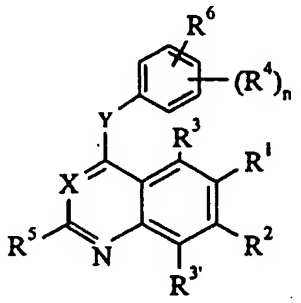
in which A to E are nitrogen or carbon and at least one of A to E is nitrogen; or two adjacent atoms together are N, O or S; R_1 is H or alkyl and n is 0, 1 or 2; m is 0 to 3 and R_2 includes optionally substituted alkyl, alkoxy, cycloalkoxy, cycloalkoxy, or two R_2 groups together form a carbocycle or heterocycle. The compounds are said to inhibit epidermal growth factor receptor tyrosine kinase and suggested uses include the treatment of cancer, psoriasis, kidney disease, pancreatitis and contraception.

WO 96/07657 discloses pyrimido[5,4-d]pyrimidine derivatives of formula



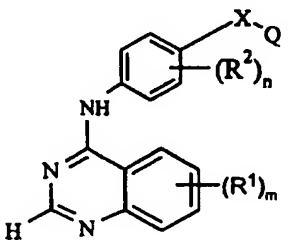
wherein Ra includes hydrogen or alkyl; Rb includes optionally substituted phenyl; and Rc includes hydrogen, halo, alkyl, cycloalkyl, cycloalkylalkylaryl, aralkyl, OH, optionally substituted alkoxy, cycloalkoxy, aryloxy, aralkoxy, mercapto, optionally substituted alkyl- or arylsulfenyl, -sulfinyl, or -sulfonyl and substituted alkyleneimino; as EGF-R inhibitors.

WO 96/09294 discloses quinoline and quinazoline derivatives of formula



wherein X is N or CH; Y includes O, S, CH_2O and NH; R^6 includes phenoxy, benzyloxy, benzylmercapto, benzylamino, benzyl, anilino, benzoyl, anilinocarbonyl, anilinomethyl, phenylethynyl, phenylethenyl, phenylethyl, phenylthio, phenylsulphonyl, benzylthio, benzylsulphonyl, phenylthiomethyl, phenylsulphonylmethyl, phenoxymethyl, thienylmethoxy, furanylmethoxy, cyclohexyl, and cyclohexylmethoxy; and R^1, R^2, R^3 and $R^{3'}$ include a range of possible substituents, predominantly not including heterocyclic ring systems; as protein receptor tyrosine kinase inhibitors, in particular as c-erbB-2 and/or p56lck inhibitors.

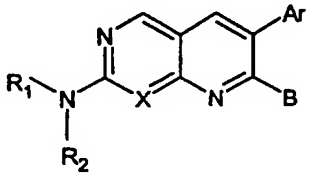
WO 96/15118 discloses quinazoline derivatives of formula



wherein X includes O, S, SO, SO_2, CH_2, OCH_2, CH_2O and CO; Q includes a phenyl or naphthyl group and various 5- or 6-membered heteroaryl moieties; n is 0, 1, 2 or 3

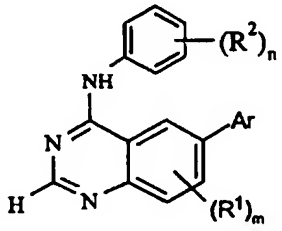
and each R^2 is independently halogeno, trifluoromethyl, hydroxy, amino, nitro, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino, diC_{1-4} alkyl amino or C_{2-4} alkanoylamino; m is 1, 2 or 3 and R^1 includes a range of possible substituents, predominantly not including heterocyclic ring systems; as receptor tyrosine kinase inhibitors, in particular as EGF-R inhibitors.

WO 96/15128 discloses pyrido[2,3-d]pyrimidine and naphthyridine derivatives of formula



wherein X is CH or N; B is halo, hydroxy or NR_3R_4; Ar includes unsubstituted and substituted phenyl or pyridyl; and R_1, R_2, R_3 and R_4 independently include hydrogen, amino, C_{1-8}alkylamino, di-C_{1-8}alkylamino, unsubstituted and substituted aromatic or heteroaromatic groups, and unsubstituted and substituted C_{1-8}alkyl, C_{2-8}alkenyl or C_{2-8}alkynyl groups.

WO 96/16960 discloses quinazoline derivatives of formula



wherein m is 1 or 2; each R^1 independently includes hydrogen and C_{1-4}alkoxy; n is 1, 2 or 3; each R^2 independently includes hydrogen, halogeno and C_{1-4}alkyl, or R^2 is an aryl- or heteroaryl-containing group, including pyridylmethoxy and benzoyl; and Ar includes a substituted or unsubstituted 5- or 9-membered nitrogen-linked heteroaryl moiety containing up to four nitrogen atoms, in particular imidazol-1-yl, imidazolin-1-yl, benzimidazol-1-yl, pyrazol-1-yl and 1,2,4-triazol-1-yl; as receptor tyrosine kinase inhibitors, in particular as EGF-R inhibitors.

It is therefore a general object of the present invention to provide compounds suitable for the treatment of disorders mediated by protein tyrosine kinase activity, and in particular treatment of the above mentioned disorders.

In addition to the treatment of tumours, the present invention envisages that other disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition, including preferential inhibition, of the appropriate protein tyrosine kinase activity.

Broad spectrum inhibition of protein tyrosine kinase may not always provide optimal treatment of, for example tumours, and could in certain cases even be detrimental to subjects since protein tyrosine kinases provide an essential role in the normal regulation of cell growth.

It is another object of the present invention to provide compounds which preferentially inhibit protein tyrosine kinases, such as EGFr, c-erbB-2, c-erbB-4, c-met, tie-2, PDGFr, c-src, lck, Zap70, and fyn. There is also perceived to be a benefit in the preferential inhibition involving small groups of protein tyrosine kinases, for example c-erbB-2 and c-erbB-4 or c-erbB-2, c-erbB-4 and EGF-R.

A further object of the present invention is to provide compounds useful in the treatment of protein tyrosine kinase related diseases which minimise undesirable side-effects in the recipient.

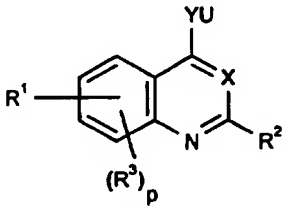
The present invention relates to heterocyclic compounds which may be used to treat disorders mediated by protein tyrosine kinases and in particular have anti-cancer properties. More particularly, the compounds of the present invention are potent inhibitors of protein tyrosine kinases such as such as EGFr, c-erbB-2, c-erbB-4, c-met, tie-2, PDGFr, c-src, lck, Zap70, and fyn, thereby allowing clinical management of particular diseased tissues.

The present invention envisages, in particular, the treatment of human malignancies, for example breast, non-small cell lung, ovary, stomach, and pancreatic tumours, especially those driven by EGFr or erbB-2, using the compounds of the present

invention. For example, the invention includes compounds which are highly active against the c-erbB-2 protein tyrosine kinase often in preference to the EGF receptor kinase hence allowing treatment of c-erbB-2 driven tumours. However, the invention also includes compounds which are highly active against both c-erbB-2 and EGF-R receptor kinases hence allowing treatment of a broader range of tumours.

More particularly, the present invention envisages that disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition of the appropriate protein tyrosine kinase activity in a relatively selective manner, thereby minimising potential side effects.

Accordingly, the present invention provides a compound of formula (I):



(I)

or a salt thereof;

wherein X is N or CH;

Y is a group $W(CH_2)$, $(CH_2)W$, or W, in which W is O, $S(O)_m$ wherein m is 0, 1 or 2, or NR^a wherein R^a is hydrogen or a C_{1-8} alkyl group;

R^1 represents a phenyl group or a 5- or 6-membered heterocyclic ring containing 1 to 4 heteroatoms selected from N, O or $S(O)_m$, wherein m is as defined above, with the provisos that the ring does not contain two adjacent O or $S(O)_m$ atoms and that where the ring contains only N as heteroatom(s) the ring is C-linked to the quinazoline or quinoline ring, R^1 being optionally substituted by one or more R^3 groups;

each R^3 is independently selected from the group comprising amino, hydrogen, halogen, hydroxy, nitro, carboxy, formyl, cyano, trifluoromethyl, trifluoromethoxy, carbamoyl, ureido, guanidino, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-8} cycloalkoxyl, C_{4-8} alkylcycloalkoxy, C_{1-8} alkylcarbonyl, C_{1-8} alkoxycarbonyl, N-C_{1-4} alkylcarbamoyl, N,N-di-[C_{1-4} alkyl]carbamoyl, hydroxyamino, C_{1-4} alkoxyamino, C_{2-4} alkanoyloxyamino, C_{1-4} alkylamino, di[C_{1-4} alkyl]amino, di-[C_{1-4} alkyl]amino-C_{1-4} alkylene-(C_{1-4} alkyl)amino, C_{1-4} alkylamino- C_{1-4} alkylene-(C_{1-4} alkyl)amino, hydroxy-C_{1-4} alkylene-(C_{1-4} alkyl)amino, phenyl, phenoxy, 4-pyridon-1-yl, pyrrolidin-1-yl, imidazol-1-yl, piperidino, morpholino, thiomorpholino, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, piperazin-1-yl, 4-C_{1-4} alkylpiperazin-1-yl, dioxolanyl, C_{1-8} alkylthio, arylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, arylsulphonyl, arylsulphinyl, halogeno-C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, C_{2-4} alkanoyloxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4} alkyl, carboxy-C_{1-4} alkyl, formyl-C_{1-4} alkyl, C_{1-4} alkoxycarbonyl-C_{1-4}-alkyl, carbamoyl-C_{1-4} alkyl, N-C_{1-4} alkylcarbamoyl-C_{1-4}alkyl, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4}alkyl, amino-C_{1-4} alkyl, C_{1-4} alkylamino-C_{1-4} alkyl, di-[C_{1-4} alkyl]amino-C_{1-4} alkyl, phenyl-C_{1-4} alkyl, 4-pyridon-1-yl-C_{1-4} alkyl, pyrrolidin-1-yl-C_{1-4} alkyl, imidazol-1-yl-C_{1-4} alkyl, piperidino-C_{1-4} alkyl, morpholino-C_{1-4} alkyl, thiomorpholino-C_{1-4} alkyl, thiomorpholino-1-oxide-C_{1-4}alkyl, thiomorpholino-1,1-dioxide-C_{1-4}alkyl, piperazin-1-yl-C_{1-4}alkyl, 4-C_{1-4} alkylpiperazin-1-yl-C_{1-4} alkyl, hydroxy-C_{2-4} alkoxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkoxy-C_{1-4} alkyl, hydroxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkylthio-C_{1-4} alkyl, C_{1-4} alkylsulphinyl-C_{1-4} alkyl, C_{1-4} alkylsulphonyl-C_{1-4} alkyl, hydroxy-C_{2-4} alkylthio-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylthio-C_{1-4} alkyl, phenoxy-C_{1-4} alkyl, anilino-C_{1-4} alkyl, phenylthio-C_{1-4} alkyl, cyano-C_{1-4} alkyl, halogeno-C_{2-4} alkoxy, hydroxy-C_{2-4} alkoxy, C_{2-4} alkanoyloxy-C_{2-4} alkoxy, C_{1-4} alkoxy-C_{2-4} alkoxy, carboxy-C_{1-4} alkoxy, formyl-C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl-C_{1-4} alkoxy, carbamoyl-C_{1-4} alkoxy, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkoxy, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkoxy, amino-C_{2-4} alkoxy, C_{1-4} alkylamino-C_{2-4} alkoxy, di-[C_{1-4} alkyl]amino-C_{2-4} alkoxy, di-[C_{1-4} alkyl-C_{2-4} alkoxy]amino-C_{2-4} alkoxy, C_{2-4} alkanoyloxy, hydroxy-C_{2-4} alkanoyloxy, C_{1-4}alkoxy-C_{2-4} alkanoyloxy, phenyl-C_{1-4} alkoxy, phenoxy-C_{2-4} alkoxy, anilino-C_{2-4} alkoxy, phenylthio-C_{2-4} alkoxy, 4-pyridon-1-yl-C_{2-4} alkoxy, piperidino-C_{2-4} alkoxy, morpholino-C_{2-4} alkoxy, thiomorpholino-C_{2-4} alkoxy, thiomorpholino-1-oxide-C_{2-4} alkoxy, thiomorpholino-1,1-dioxide-C_{2-4} alkoxy, piperazin-1-yl-C_{2-4} alkoxy, 4-C_{1-4} alkylpiperazin-1-yl-C_{2-4} alkoxy, pyrrolidin-1-yl-C_{2-4} alkoxy, imidazol-1-yl-C_{2-4}

alkoxy, halogeno-C_{2-4} alkylamino, hydroxy-C_{2-4} alkylamino, C_{2-4} alkanoyloxy-C_{2-4} alkylamino, C_{1-4} alkoxy-C_{2-4} alkylamino, carboxy-C_{1-4} alkylamino, C_{1-4} alkoxycarbonyl-C_{1-4} alkylamino, carbamoyl-C_{1-4} alkylamino, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkylamino, amino-C_{2-4} alkylamino, C_{1-4} alkylamino-C_{2-4} alkylamino, di-[C_{1-4}alkyl]amino-C_{2-4} alkylamino, phenyl-C_{1-4} alkylamino, phenoxy-C_{2-4} alkylamino, anilino-C_{2-4} alkylamino, 4-pyridon-1-yl- C_{2-4} alkylamino, pyrrolidin-1-yl-C_{2-4} alkylamino, imidazol-1-yl-C_{2-4} alkylamino, piperidino-C_{2-4} alkylamino, morpholino-C_{2-4} alkylamino, thiomorpholino-C_{2-4} alkylamino, thiomorpholino-1-oxide-C_{2-4} alkylamino, thiomorpholino-1,1-dioxide-C_{2-4} alkylamino, piperazin-1-yl-C_{2-4}alkylamino, 4-(C_{1-4}alkyl)piperazin-1-yl-C_{2-4}alkylamino, phenylthio-C_{2-4} alkylamino, C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonylamino, C_{1-4} alkylsulphonylamino, C_{1-4} alkylsulphinylamino, benzamido, benzenesulphonamido, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, halogeno-C_{2-4} alkanoylamino, hydroxy-C_{2-4} alkanoylamino, hydroxy-C_{2-4} alkanoyl-(C_{1-4} alkyl)-amino, C_{1-4} alkoxy-C_{2-4} alkanoylamino, carboxy-C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonyl-C_{2-4} alkanoylamino, carbamoyl-C_{2-4} alkanoylamino, N-C_{1-4} alkylcarbamoyl-C_{2-4} alkanoylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{2-4} alkanoylamino, amino-C_{2-4} alkanoylamino, C_{1-4} alkylamino-C_{2-4} alkanoylamino or di-[C_{1-4} alkyl]amino-C_{2-4} alkanoylamino; and wherein said benzamido or benzenesulphonamido substitutent or any anilino, phenoxy or phenyl group on a R^3 substituent may optionally bear one or two halogeno, C_{1-4} alkyl or C_{1-4} alkoxy substituents; and wherein any substituent containing a heterocyclic ring may optionally bear one or two halogeno, C_{1-4} alkyl or C_{1-4} alkoxy substituents on said ring; and wherein any substituent containing a heterocyclic ring may optionally bear one or two oxo or thioxo substituents on said ring;

or R^3 represents a group selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 wherein

M^1 represents a C_{1-4} alkyl group, wherein optionally a CH_2 group is replaced by a CO group;

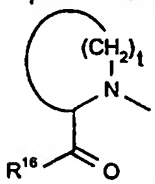
M^2 represents NR^{12} or $CR^{12}R^{13}$, in which R^{12} and R^{13} each independently represent H or C_{1-4} alkyl;

M^3 represents a C_{1-4} alkyl group;

$M^{3'}$ represents a C_{1-4} alkyl group or is absent;

M^4 represents CN, $NR^{12}S(O)_mR^{13}$, $S(O)_mNR^{14}R^{15}$, $CONR^{14}R^{15}$, $S(O)_mR^{13}$ or CO_2R^{13}, in which R^{12}, R^{13} and m are as hereinbefore defined and R^{14} and R^{15} each independently represent H or C_{1-4} alkyl, or R^{14} and R^{15} together with the nitrogen atom to which they are attached represent a 5-or 6-membered ring optionally containing 1 or 2 additional heteroatoms selected from N, O or $S(O)_m$ in which ring any nitrogen atom present may optionally be substituted with a C_{1-4} alkyl group, and which ring may optionally bear one or two oxo or thioxo substituents;

M^5 represents the group $NR^{14}R^{15}$, wherein R^{14} and R^{15} are as defined above, or M^5 represents the group



in which t represents 2 to 4 and R^{16} represents OH, OC_{1-4} alkyl or $NR^{14}R^{15}$; and

M^6 represents a C_{3-6} cycloalkyl group, the group $NR^{14}R^{15}$, wherein R^{14} and R^{15} are as defined above, or a 5- or 6-membered heterocyclic ring system containing 1 to 4 heteroatoms selected from N, O or S;

and p is 0 to 3; or when p is 2 or 3, two adjacent R^3 groups together form an optionally substituted methylenedioxy or ethylenedioxy group;

R^2 is selected from the group comprising hydrogen, halogen, trifluoromethyl, C_{1-4} alkyl and C_{1-4} alkoxy;

U represents phenyl or a 5 to 10-membered mono or bicyclic ring system in which one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and $S(O)_m$, wherein m is 0,1 or 2, and wherein U is substituted by at least one independently selected R^6 group and is optionally substituted by at least one independently selected R^4 group;

each R^4 is independently hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino, di-[C_{1-4} alkyl]amino, C_{1-4} alkylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbamoyl, di-[C_{1-4} alkyl] carbamoyl, carbamyl, C_{1-4} alkoxycarbonyl, cyano, nitro or trifluoromethyl;

each R^6 is independently a group ZR^7 wherein Z is joined to R^7 through a $(CH_2)p$ group in which p is 0, 1 or 2 and Z represents a group $V(CH_2)$, $V(CF_2)$, $(CH_2)V$, $(CF_2)V$, V(CRR'), V(CHR) or V where R and R' are each C_{1-4} alkyl and in which V is a hydrocarbyl group containing 0,1 or 2 carbon atoms, carbonyl, dicarbonyl, CH(OH), CH(CN), sulphonamide, amide, O, $S(O)_m$ or NR^b where R^b is hydrogen or R^b is C_{1-4} alkyl; and R^7 is an optionally substituted C_{3-6} cycloalkyl; or an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety;
or R^6 is a group ZR^7 in which Z is NR^b, and NR^b and R^7 together form an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety.

Solvates of the compounds of formula (I) are also included within the scope of the present invention.

Heterocyclic groups comprise one or more rings which may be saturated, unsaturated, or aromatic and which may independently contain one or more heteroatoms in each ring.

Carbocyclic groups comprise one or more rings which may be independently saturated, unsaturated, or aromatic and which contain only carbon and hydrogen.

Suitably the 5, 6, 7, 8, 9 or 10-membered heterocyclic moiety is selected from the group comprising: furan, dioxolane, thiophene, pyrrole, imidazole, pyrrolidine, pyran, pyridine, pyrimidine, morpholine, piperidine, oxazole, isoxazole, oxazoline, oxazolidine, thiazole, isothiazole, thiadiazole, benzofuran, indole, isoindole, quinazoline, quinoline, isoquinoline and ketal.

Suitably the 5, 6, 7, 8, 9 or 10-membered carbocyclic moiety is selected from the group comprising: phenyl, benzyl, indene, naphthalene, tetralin, decalin, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl and cycloheptyl.

By halo is meant fluoro, chloro, bromo or iodo.

Alkyl groups containing three or more carbon atoms may be straight, branched or cyclised.

In an embodiment R^3 is as defined above with the exception of wherein any substituent containing a heterocyclic ring bears one or two oxo or thioxo substituents on said ring, and with the exception of C_{1-4} alkylsulphinyl-C_{1-4} alkyl or C_{1-4} alkylsulphonyl-C_{1-4} alkyl; and R^{14} and R^{15} are as defined above with the exception of wherein they together with the nitrogen atom to which they are attached represent a 5- or 6-membered ring and said ring bears one or two oxo or thioxo substituents; save that R^3 may represent 4-pyridon-1-yl, 4-pyridon-1-yl-C_{1-4} alkyl, 4-pyridon-1-yl-C_{2-4} alkoxy, 4-pyridon-1-yl-C_{2-4} alkylamino, 2-oxopyrrolidin-1-yl or 2,5-dioxopyrrolidin-1-yl.

In an embodiment, X is N.

In a further embodiment, Y is NR^b, $NR^b(CH_2)$, or $(CH_2)NR^b$, preferably Y is NR^b and R^b is preferably hydrogen or methyl.

In a further embodiment R^1 is a phenyl group or a 5- or 6-membered heterocyclic ring as defined above substituted with an R^3 group as defined above; and p = 0.

In a preferred embodiment R^1 is a 5- or 6-membered heterocyclic ring as defined above substituted by one or more R^3 groups selected from the group comprising amino, hydrogen, halogen, hydroxy, formyl, carboxy, cyano, nitro, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, C_{1-8} alkylsulphinyl, C_{1-8} alkylsulphonyl, C_{1-4} alkylamino, C_{1-4} dialkylamino, dioxolanyl, hydroxy-C_{1-4} alkyl or hydroxy-C_{1-4} alkanoyl -(C_{1-4} alkyl)-amino.

In a further preferred embodiment R^1 is a 5- or 6-membered heterocyclic ring as defined above substituted by one or more R^3 groups selected from the group comprising C_{1-4}alkyl, C_{1-4}alkylamino-C_{1-4}alkyl, di(C_{1-4}alkyl)amino-C_{1-4} alkyl, formyl, carboxy, C_{1-4}alkoxycarbonyl, dioxolanyl or trifluoromethyl.

In a further preferred embodiment R^1 is a 5- or 6-membered heterocyclic ring as defined above substituted by one or more R^3 groups selected from the group C_{1-4}alkylsulphinyl-C_{1-4}alkyl or C_{1-4}alkylsulphonyl-C_{1-4}alkyl.

In a further preferred embodiment R^1 is a 5- or 6-membered heterocyclic ring as defined above substituted with an R^3 group selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined above; and p = 0.

In a further preferred embodiment R^1 is a 5- or 6-membered heterocyclic ring as defined above substituted with an R^3 group selected from piperidonyl-methyl, pyrrolidinonyl-methyl or dioxoimidazolidinyl-methyl.

In a further embodiment the group M^2-M^3-M^4 represents an α-, β- or γ-amino carboxylic, sulphinic or sulphonic acid or a C_{1-4} alkyl ester, an amide or a C_{1-4} alkyl- or di-(C_{1-4} alkyl)-amide thereof.

Preferably M^1 represents CH_2, CO, CH_2CH_2 or CH_2CO, more preferably CH_2.

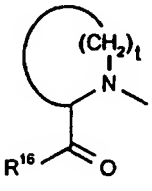
Preferably M^2 represents NR^{12} in which R^{12} is as defined above; more preferably R^{12} represents H or methyl.

Preferably M^3 represents CH_2, CH_2CH_2 or propyl.

Preferably $M^{3'}$ represents CH_2, ethyl, propyl, isopropyl or is absent.

Preferably M^4 represents SOR^{13}, SO_2R^{13}, $NR^{12}SO_2R^{13}$, $SO_2NR^{14}R^{15}$, CO_2R^{13} or $CONR^{14}R^{15}$ in which R^{12} and R^{13} are defined above and R^{14} and R^{15} each independently represent H or C_{1-4} alkyl; more preferably R^{12}, R^{13}, R^{14} and R^{15} each independently represent H or methyl.

Preferably M^5 represents a group $NR^{14}R^{15}$ in which R^{14} and R^{15} together with the nitrogen atom to which they are attached represent a 6-membered ring optionally containing an additional heteroatom selected from N or O, in which ring any nitrogen atom present may optionally be substituted with a C_{1-4} alkyl group, preferably a methyl group; or M^5 represents a group



in which t represents 2 or 3 and R^{16} represents OH, NH_2, $N(C_{1-4}$ alkyl$)_2$ or OC_{1-4} alkyl; more preferably R^{16} represents NH_2 or $N(CH_3)_2$.

Preferably M^5 also represents a group $NR^{14}R^{15}$ in which R^{14} and R^{15} together with the nitrogen atom to which they are attached represent a 5- or 6-membered ring optionally containing an additional heteroatom selected from N or O, in which ring any nitrogen atom present may optionally be substituted with a C_{1-4} alkyl group, preferably a methyl group, and which ring also bears one or two oxo substituents.

Preferably M^6 represents a group $NR^{14}R^{15}$ in which R^{14} and R^{15} each independently represent C_{1-4} alkyl, more preferably methyl, or R^{14} and R^{15} together with the nitrogen atom to which they are attached represent a 5- or 6-membered ring optionally containing an additional heteroatom selected from N or O, in which ring any nitrogen atom present may optionally be substituted with a C_{1-4} alkyl group, preferably a methyl group; or M^6 represents a 5- or 6-membered heterocyclic ring system containing 1 or 2 heteroatoms selected from N or O.

In a further preferred embodiment M^2-M^3-M^4 represents an α-amino carboxylic acid or a methyl ester or amide thereof.

In a further preferred embodiment M^2-M^3-M^4 represents an α-, β- or γ-amino sulphinic or sulphonic acid, more preferably a β- or γ-amino sulphinic or sulphonic acid, most preferably a β-aminosulphonic acid, or a methyl ester thereof.

In an especially preferred embodiment M^2-M^3-M^4 represents a methylsulphonylethylamino, methylsulphinylethylamino, methylsulphonylethyl(methylamino), methylsulphinylethyl(methylamino), methylsulphonylpropylamino, methylsulphinylpropylamino, methylsulphonamidoethylamino, aminosulphonylethylamino, methylaminosulphonylethylamino, sarcosinamide, glycine, glycinamide, glycine methyl ester or acetylaminoethylamino group.

In a further especially preferred embodiment M^5 represents a piperazinyl, methylpiperazinyl, piperidinyl, pyridyl, prolinamido or *N,N*-dimethylprolinamido group.

In a further especially preferred embodiment M^5 represents a piperidonyl, pyrrolidinonyl or dioxoimidazolidinyl group.

In a further especially preferred embodiment M^5 represents an isopropylamino or N-morpholinyl group.

In a further especially preferred embodiment M^1-M^5 represents an isopropylacetamido or N-morpholinoacetamido group.

In a further especially preferred embodiment M^1-M^5 represents a piperidonyl-methyl, pyrrolidinonyl-methyl or dioxoimidazolidinyl-methyl group.

In a further especially preferred embodiment M^2-$M^{3'}$-M^6 represents a pyridylamino, cyclopropylamino, N-(piperidin-4-yl)-N-methylamino, N,N-dimethylaminoprop-2-ylamino, N-(2-dimethylaminoethyl)-N-ethylamino or tetrahydrofuranomethylamino group, preferably a pyridylamino group.

In an embodiment R^1 may be selected from the group comprising phenyl, furan, thiophene, pyridine, pyrimidine, pyrazine, pyrrole, oxazole, isoxazole, oxadiazole, thiazole, isothiazole, triazole, tetrazole and imidazole or a hydrogenated derivative of any of the aforementioned.

In a further preferred embodiment R^1 may be selected from the group comprising furan, dihydrofuran, thiophene, imidazole, tetrazole, triazole, pyridine, pyrrole, pyrimidine, isoxazole or oxadiazole.

In a further preferred embodiment R^1 is an oxadiazolidinone ring.

In an especially preferred embodiment R^1 is selected from the group comprising furan, imidazole, oxadiazole (particularly 1,3,4-oxadiazole and 1,2,4-oxadiazole) and triazole (particularly 1,2,3-triazole and 1,3,4-triazole).

In an embodiment R^2 is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy or halogen, preferably methyl or hydrogen, more preferably hydrogen.

In a further embodiment R^4 is hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, di-[C_{1-4} alkyl]amino, nitro or trifluoromethyl, preferably hydrogen, halogen or methyl, more preferably hydrogen.

In a preferred embodiment R^7 is an optionally substituted phenyl, dioxolanyl, thienyl, cyclohexyl or pyridyl group.

In a further embodiment, Z is absent or represents oxygen, CH_2, NR^b, $NR^b(CH_2)$, $(CH_2)NR^b$, $CH(CH_3)$, $O(CH_2)$, $(CH)CN$, $O(CF_2)$, $(CH_2)O$, $(CF_2)O$, $S(CH_2)$, $S(O)_m$, carbonyl or dicarbonyl, wherein R^b is hydrogen or C_{1-4} alkyl.

In a preferred embodiment Z is oxygen, dicarbonyl, OCH_2, $CH_2(CN)$, $S(O)_m$ or NR^b, wherein R^b is hydrogen or C_{1-4} alkyl.

In a further preferred embodiment R^6 is benzyl, , halo-, dihalo- and trihalobenzyl, α-methylbenzyl, phenyl, halo-, dihalo- and trihalophenyl, pyridyl, pyridylmethyl, pyridyloxy, pyridylmethoxy, thienylmethoxy, dioxolanylmethoxy, cyclohexylmethoxy, phenoxy, halo-, dihalo- and trihalophenoxy, phenylthio, benzyloxy, halo-, dihalo- and trihalobenzyloxy, C_{1-4} alkoxybenzyloxy, phenyloxalyl or benzenesulphonyl, more preferably benzyl, fluorobenzyl, difluorobenzyl, benzyloxy, fluorobenzyloxy, pyridylmethyl, phenyl, benzenesulphonyl, phenoxy or fluorophenoxy.

In a further embodiment R^6 is in the para position with respect to Y.

When the group Z is absent, $R^6 = R^7$.

One or both of the rings comprising the mono or bicyclic ring system U may be aromatic or non-aromatic. The R^4 and R^6 groups may be bound to the ring system

by either a carbon atom or a heteroatom of the ring system. The ring system itself may be bound to the bridging group by a carbon atom or a heteroatom. The R^4 and R^6 groups may be bound to either ring when U represents a bicyclic ring system, but these groups are preferably bound to the ring which is not bound to the bridging group Y in such a case.

Examples of suitable mono or bicyclic groups U include: phenyl, isoindenyl, indenyl, indanyl, naphthyl, 1,2-dihydronaphthyl or 1,2,3,4-tetrahydronaphthyl, pyrrolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furanyl, 2H-pyranyl, thiophenyl, 1H-azepinyl, oxepinyl, thiepinyl, azocinyl, 2H-oxocinyl, thieno[2,3-b] furanyl, thianaphthenyl, indolyl, indolinyl, isoindolyl, isoindolinyl, indolizinyl, 1H-benzimidazolyl, 2,3-dihydro-1H-benzimidazolyl, 1H-indazolyl, 2,3-dihydro-1H-indazolyl, benzoxazolyl, 2,3-dihydrobenzoxazolyl, benzo[c]isoxazolyl, benzo[d]isoxazolyl, 2,3-dihydrobenzo[d]isoxazolyl, benzothiazoyl, 2,3-dihydrobenzothiazolyl, benzo[c]isothiazolyl, benzo[d]isothiazolyl, 2,3-dihydrobenzo[d]isothiazolyl, 1H-benzotriazolyl, benzo[c]furanyl, benzo[c][1,2,3]thiadiazolyl, benzo[d][1,2,3]oxadiazolyl, benzo[d][1,2,3]thia-diazolyl, quinolyl, 1,2-dihydroquinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolyl 1,2,3,4-tetrahydroisoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, 4H-1,4-benzoxazinyl, 2,3-dihydro-4H-1,4-benzoxazinyl, 4H-1,4-benzothiazinyl or 2,3-dihydro-4H-1,4-benzothiazinyl.

Suitably U represents a phenyl, indolyl, isoindolyl, indolinyl, isoindolinyl, 1H-indazolyl, 2,3-dihydro-1H-indazolyl, 1H-benzimidazolyl, 2,3-dihydro-1H-benzimidazolyl or 1H-benzotriazolyl group.

In an embodiment, the optional substitutents for the carbocyclic or heterocyclic moiety, which may be present at any available position of said moiety, are selected from the group comprising:

$(CH_2)_qS(O)_m$-C_{1-4}alkyl, $(CH_2)_qS(O)_m$-C_{3-6}cycloalkyl, $(CH_2)_qSO_2NR^8R^9$, $(CH_2)_qNR^8R^9$, $(CH_2)_qCO_2R^8$, $(CH_2)_qOR^8$, $(CH_2)_qCONR^8R^9$, $(CH_2)_qNR^8COR^9$, $(CH_2)_qCOR^8$, $(CH_2)_qR^8$, $NR^8SO_2R^9$ and $S(O)_mR^8$,

wherein q is an integer from 0 to 4 inclusive; m is 0,1 or 2;

R^8 and R^9 are independently selected from the group comprising hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, a 5- or 6-membered saturated or unsaturated heterocyclic ring which may be the same or different and which contains one or more heteroatoms which are selected from N, O or $S(O)_m$, with the proviso that the heterocyclic ring does not contain two adjacent O or $S(O)_m$ atoms.

In a further embodiment the optional substitutents for the carbocyclic or heterocyclic moiety are selected from the group comprising morpholine, piperazine, piperidine, pyrrolidine, tetrahydrofuran, dioxolane, oxothiolane and oxides thereof, dithiolane and oxides thereof, dioxane, pyridine, pyrimidine, pyrazine, pyridazine, furan, thiofuran, pyrrole, triazine, imidazole, triazole, tetrazole, pyrazole, oxazole, oxadiazole and thiadiazole.

Other optional substituents for the carbocyclic or heterocyclic moiety and also for other optionally substituted groups include, but are not limited to, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, nitro, amino, cyano, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkyl carbonyl, carboxylate and C_{1-4} alkoxy carboxyl.

In a further embodiment X represents N; p is 0; and the group R^1 is in the 6-position of the quinazoline ring system.

In a preferred embodiment of the present invention there is provided a compound of formula (I) or a salt or solvate thereof wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; R^1 represents furan, thiophene, pyrrole, pyridine, pyrimidine, pyrazine, imidazole, oxazole, isoxazole, oxadiazole, tetrazole, triazole, dioxolane or a partially or fully hydrogenated derivative of any of these groups, optionally substituted by one or more R^3 groups selected from halo, trifluoromethyl, C_{1-4} alkyl, carboxy, C_{1-4}-alkoxycarbonyl, formyl, hydroxy-C_{1-4} alkyl, 1,3-dioxolan-2-yl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy-C_{1-4}alkanoyl-(C_{1-4}alkyl)-amino, C_{1-4} alkylamino-C_{1-4} alkyl or di(C_{1-4} alkyl)amino-C_{1-4} alkyl; p is 0; R^2 represents hydrogen; R^4 represents hydrogen, halo or methyl; U represents phenyl, indolyl, benzimidazolyl or indazolyl, more preferably phenyl or indazolyl; and R^6 represents phenyl, benzyl, α-methylbenzyl, fluorobenzyl, difluorobenzyl, pyridylmethyl, benzenesulphonyl, phenoxy, fluorophenoxy, benzyloxy or fluorobenzyloxy.

In a further preferred embodiment of the present invention there is provided a compound of formula (I) or a salt or solvate thereof wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; R^1 represents furan, thiophene, pyrrole, pyridine, pyrimidine, pyrazine, imidazole, oxazole, isoxazole, oxadiazole, tetrazole, triazole, dioxolane or a partially or fully hydrogenated derivative of any of these groups substituted by a C_{1-4}alkylsulphinyl-C_{1-4}alkyl or C_{1-4}alkylsulphonyl-C_{1-4}alkyl group; p is 0; R^2 represents hydrogen; R^4 represents hydrogen, halo or methyl; U represents phenyl, indolyl, benzimidazolyl or indazolyl, more preferably phenyl or indazolyl; and R^6 represents phenyl, benzyl, α-methylbenzyl, fluorobenzyl, difluorobenzyl, pyridylmethyl, benzenesulphonyl, phenoxy, fluorophenoxy, benzyloxy or fluorobenzyloxy.

In further preferred embodiment of the present invention there is provided a compound of formula (I) or a salt or solvate thereof wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; R^1 represents furan, thiophene, pyrrole, pyridine, pyrimidine, pyrazine, imidazole, oxazole, isoxazole, oxadiazole, tetrazole, triazole, dioxolane or a partially or fully hydrogenated derivative of any of these groups, optionally substituted with an R^3 group selected from methylsulphonylethylaminomethyl, methylsulphonylethylamino-carbonyl, methylsulphinylethylamino-methyl, methylsulphinylethylamino-carbonyl, methylsulphonylpropylamino-methyl, methylsulphinylpropylamino-methyl, methylsulphonylpropyamino-carbonyl, methylsulphinylpropylamino-carbonyl, methylsulphonylethyl-(methylamino)-methyl, methylsulphonylethyl-(methylamino)-carbonyl, methylsulphinylethyl-(methylamino)-methyl, methylsulphinylethyl-(methylamino)-carbonyl, methylsulphonylpropyl-(methylamino)-methyl, methylsulphinylpropyl-(methylamino)-methyl, methylsulphonylpropyl-(methylamino)-carbonyl, methylsulphinylpropyl-(methylamino)-carbonyl, methylsulphonamidoethylamino-methyl, methylsulphonamidopropylamino-methyl, aminosulphonylethylaminomethyl, methylaminosulphonylethylaminomethyl, sarcosinamidomethyl, glycinylmethyl, glycinamidomethyl, glycinylmethyl methyl ester, acetylaminoethylaminomethyl, piperazinylmethyl, methylpiperazinylmethyl, piperidinylmethyl, pyridylmethyl, N-(prolinamido)methyl, (N,N-dimethyl-prolinamido)methyl, pyridylaminomethyl, cyclopropylaminomethyl, N-(piperidin-4-yl)-N-methylaminomethyl, N,N-dimethylaminoprop-2-ylaminomethyl, N-(2-

dimethylaminoethyl)-N-ethylaminomethyl, isopropylacetamido, N-morpholinylacetamido or tetrahydrofuranomethylaminomethyl and optionally further substituted by one or more C_{1-4} alkyl groups; p is 0; R^2 represents hydrogen; R^4 represents hydrogen, halo or methyl; U represents phenyl, indolyl, benzimidazolyl or indazolyl, more preferably phenyl or indazolyl; and R^6 represents phenyl, benzyl, α-methylbenzyl, fluorobenzyl, difluorobenzyl, pyridylmethyl, benzenesulphonyl, phenoxy, fluorophenoxy, benzyloxy or fluorobenzyloxy.

In further preferred embodiment of the present invention there is provided a compound of formula (I) or a salt or solvate thereof wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; R^1 represents furan, thiophene, pyrrole, pyridine, pyrimidine, pyrazine, imidazole, oxazole, isoxazole, oxadiazole, tetrazole, triazole, dioxolane or a partially or fully hydrogenated derivative of any of these groups, substituted with an R^3 group selected from piperidonyl-methyl, pyrrolidinonyl-methyl or dioxoimidazolidinyl-methyl; p is 0; R^2 represents hydrogen; R^4 represents hydrogen, halo or methyl; U represents phenyl, indolyl, benzimidazolyl or indazolyl, more preferably phenyl or indazolyl; and R^6 represents phenyl, benzyl, α-methylbenzyl, fluorobenzyl, difluorobenzyl, pyridylmethyl, benzenesulphonyl, phenoxy, fluorophenoxy, benzyloxy or fluorobenzyloxy.

In an especially preferred embodiment of the present invention there is provided a compound of formula (I) or a salt or solvate thereof wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; R^1 represents a furan, dihydrofuran, thiophene, pyridine, pyrrole, pyrimidine, isoxazole, triazole, tetrazole, imidazole or oxadiazole ring, preferably furan, imidazole, oxadiazole and triazole, substituted with an R^3 group selected from C_{1-4}alkyl, C_{1-4}alkylamino-C_{1-4}alkyl, di(C_{1-4}alkyl)amino-C_{1-4} alkyl, formyl, carboxy, C_{1-4}alkoxycarbonyl, dioxolanyl, trifluoromethyl, methylsulphonylethylaminomethyl, methylsulphonylethylamino-carbonyl, methylsulphonylethyl(methylamino)-methyl, methylsulphonamidoethylamino-methyl, aminosulphonylethylamino-methyl, methylaminosulphonylethylamino-methyl, N,N-dimethylaminoprop-2-ylaminomethyl, N-(2-dimethylaminoethyl)-N-ethylaminomethyl, pyridylaminomethyl, tetrahydrofuranomethylaminomethyl, piperazinylmethyl, methylpiperazinylmethyl, piperidinylmethyl, pyridylmethyl, N-(prolinamido)methyl or (N,N-dimethyl-

prolinamido)methyl; p is 0; R^2 represents hydrogen; R^4 represents hydrogen or halo; U represents phenyl or indazolyl; and R^6 represents benzyl, fluorobenzyl, difluorobenzyl, pyridylmethyl, benzenesulphonyl, phenoxy, benzyloxy or fluorobenzyloxy.

In a further especially preferred embodiment of the present invention there is provided a compound of formula (I) or a salt or solvate thereof wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; R^1 represents a furan, dihydrofuran, thiophene, pyridine, pyrrole, pyrimidine, isoxazole, triazole, tetrazole, imidazole or oxadiazole ring, preferably furan, imidazole, oxadiazole and triazole, substituted with an R^3 group selected from a C_{1-4}alkylsulphinyl-C_{1-4}alkyl, C_{1-4}alkylsulphonyl-C_{1-4}alkyl, piperidonyl-methyl, pyrrolidinonyl-methyl or dioxoimidazolidinyl-methyl group; p is 0; R^2 represents hydrogen; R^4 represents hydrogen or halo; U represents phenyl or indazolyl; and R^6 represents benzyl, fluorobenzyl, difluorobenzyl, pyridylmethyl, benzenesulphonyl, phenoxy, benzyloxy or fluorobenzyloxy.

In a most especially preferred embodiment of the present invention there is provided a compound of formula (I) or a salt or solvate thereof wherein X represents N; Y represents NH; R^1 represents a furan, imidazole, oxadiazole or triazole ring optionally substituted with a methyl group; p is 0; R^2 represents hydrogen; R^4 represents hydrogen; U represents phenyl or indazolyl; and R^6 represents benzyl, fluorobenzyl, benzyloxy or fluorobenzyloxy.

In a further most especially preferred embodiment of the present invention there is provided a compound of formula (I) or a salt or solvate thereof wherein X represents N; Y represents NH; R^1 represents a furan ring substituted with an R^3 group selected from methylsulphonylethylaminomethyl, methylsulphonylethyl(methylamino)-methyl, methylsulphonamidoethylamino-methyl, aminosulphonylethylamino-methyl, methylaminosulphonylethylamino-methyl, methylpiperazinylmethyl or (prolinamido)methyl; p is 0; R^2 represents hydrogen; R^4 represents hydrogen; U represents phenyl or indazolyl; and R^6 represents benzyl, fluorobenzyl, benzyloxy or fluorobenzyloxy.

In a further most especially preferred embodiment of the present invention there is provided a compound of formula (I) or a salt or solvate thereof wherein X represents N; Y represents NH; R^1 represents an oxadiazole ring substituted with an R^3 group selected from piperidonyl-methyl or pyrrolidinonyl-methyl; p is 0; R^2 represents hydrogen; R^4 represents hydrogen; U represents phenyl or indazolyl; and R^6 represents benzyl, fluorobenzyl, benzyloxy or fluorobenzyloxy.

Preferred compounds of the present invention include:
(4-Benzyloxy-phenyl)-(6-furan-2-yl-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(thiophen-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(pyridin-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(pyrimidin-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(3-methyl-3H-imidazol-4-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(2,3-dihydrofuran-5-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(3-methyl-1,2,3-triazol-4-yl)-quinazolin-4-yl)-amine;
5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde;
(4-Benzyloxy-phenyl)-(6-(5-(4-methylpiperazin-1-ylmethyl)-furan-2-yl)- quinazolin-4-yl)-amine;
(S)-1-(5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-pyrrolidine-2-carboxylic acid amide;
N2-(5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-N1,N1-dimethyl-propane-1,2-diamine;
N-(5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-N-ethyl-N',N'-dimethyl-ethane-1,2-diamine;
(4-Benzyloxy-phenyl)-(6-(5-(pyridin-3-ylaminomethyl)-furan-2-yl)quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-(((tetrahydro-furan-2-ylmethyl)-amino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-(1,3)-dioxolan-2-yl-furan-2-yl)-quinazolin-4-yl)-amine;
5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-furan-2-carbaldehyde;
(S)-1-(5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-pyrrolidine-2-carboxylic acid amide;

(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)quinazolin-4-yl)-amine;
(1-(2-Fluorobenzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-(3-Fluorobenzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-Pyridin-2-ylmethyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-(2,3-Difluorobenzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)quinazolin-4-yl)-amine;
(3-Chloro-4-(2-fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(3-Chloro-4-(3-fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(2-Fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolinyl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-(3,5-Difluoro-benzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine
(4-(4-Fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(2-Fluoro-benzyloxy)-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(4-Fluoro-benzyloxy)-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;

(4-Pyridin-3-ylmethoxy)-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(3-methyl-3H-imidazol-4-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(1-methyl-1H-imidazol-2-yl)quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(1H-tetrazol-5-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl0-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-triazol-2-yl)-quinazolin-4-yl)-amine;
(S)-1-(2-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-3-methyl-3H-imidazol-4-ylmethyl)-pyrrolidine-2-carboxylic acid amide;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-methanesulphonylmethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(1-methylpyridinium-2-yl)quinazolin-4-yl)-amine; chloride;
(4-Benzyloxy-phenyl)-(6-(2,3-dimethyl-3H-imidazol-4-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(-6-(3-methylisoxazol-5-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-(((2-methanesulphonyl-ethyl)-methyl-amino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
N-(2-((5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-amino)-ethyl)-methanesulphonamide;
2-((5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-amino)-ethanesulphonic acid amide;
5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carboxylic acid methyl ester;
5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carboxylic acid;
5-[4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl]-furan-2-carboxylic acid (2-methanesulphonyl-ethyl)-amide;
2-((5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-amino)-ethanesulphonic acid methylamide;
(1-Benzyl-1H-indazol-5-yl)-(6-(3-methyl-1,2,4-oxadiazol-5-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-methyl-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-(2-dimethylamino-ethyl)-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-(dimethylaminomethyl)-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-(((2-methanesulphonyl-ethyl)-amino)-methyl)-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine;

(1-Benzyl-1H-indazol-5-yl)-(6-(5-methanesulphonylmethyl-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-methyl-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl0-amine;
(1-Benzyl-1H-indazol-5-yl)-6-(5-(pyridin-3-ylmethyl)-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(1-methylpyrrol-2-yl)-quinazolin-4-yl)-amine;
5-(4-(1-Benzyl-1H-indazol-5-yl)-quinazolin-6-yl)-1-methyl-pyrrole-2-carbaldehyde;
1-(3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-1,2,4-oxadiazol-5-ylmethyl)-piperidin-4-one;
1-(3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-1,2,4-oxadiazol-5-ylmethyl)-pyrrolidin-2-one;
1-(3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-1,2,4-oxadiazol-5-ylmethyl)-imidazolidin-2,5-dione;
3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-4H-1,2,4-oxadiazolidin-3-one;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesuphonyl-ethyl-amino)-methyl)-1-methyl-pyrrol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(1-(3-N,N-dimethylaminopropyl)-imidazol-5-yl)- quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazolyl)-(6-(1-(3-N,N-dimethylaminopropyl)-imidazol-5-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(1-(3-N,N-dimethylaminopropyl)-imidazol-2-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazolyl)-(6-(1-(3-N,N-dimethylaminopropyl)-imidazol-5-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-(2-Fluoro-benzyl)-1H-indazol-5-yl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-(3-Fluoro-benzyl)-1H-indazol-5-yl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-(4-Fluoro-benzyl)-1H-indazol-5-yl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(7-(5-methyl-[1,3,4]oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(7-(3-methyl-3H-imidazol-4-yl)quinazolin-4-yl)- amine;

(1-Benzyl-1H-indazol-5-yl)-[7-(furan-2-yl)-quinazolin-4-yl]-amine;
(1-Benzyl-1H-indazol-5-yl)-[7-(5-(1,3-dioxolan-2-yl)-furan-2-yl)quinazolin-4-yl] amine;
5-[4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-7-yl]-furan-2-carbaldehyde;
(1-Benzyl-1H-indazol-5-yl)-[7-{5-[(2-methanesulphonyl-ethylamino)-methyl]-furan-2-yl}-quinazolin-4-yl]-amine;
(S)-1-{5-[4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-7-yl]-furan-2-yl-methyl}-pyrrolidine-2-carboxylic acid amide;
(4-Benzyloxy-phenyl)-(6-(3-methyl-[1,2]oxazol-4-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(4-(1,3-dioxolan-2-yl)-3-methyl-3H-imidazol-2-yl)-quinazolin-4-yl)-amine;
2-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-3-methyl-3H-imidazol-4-carbaldehyde;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

Other preferred compounds of the present invention include:
(4-Benzyloxy-phenyl)-(6-(imidazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-[5-(4-methyl-piperazinylmethyl)-1-methylimidazol-2-yl]-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-[5-(*N*,*N*-dimethylaminomethyl)-1-methylimidazol-2-yl]-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-[5-(4-methyl-piperazinylmethyl)-imidazol-2-yl]-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-[5-(*N*,*N*-dimethylaminomethyl)-imidazol-2-yl]-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-[1-(4-methyl-piperazinylmethyl)-imidazol-2-yl]-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-[1-(*N*,*N*-dimethylaminomethyl)-imidazol-2-yl]-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-carboxymethylaminomethyl-furan-2-yl)-quinazolin-4-yl)-amine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

Particularly preferred compounds of the present invention include:

(4-Benzyloxy-phenyl)-(6-furan-2-yl-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(3-methyl-3H-imidazol-4-yl)-quinazolin-4-yl)-amine;
(4-(4-Fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-triazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-methyl-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

Further particularly preferred compounds of the present invention include:
(4-Benzyloxy-phenyl)-(6-(5-(4-methylpiperazin-1-ylmethyl)-furan-2-yl)- quinazolin-4-yl)-amine;
(S)-1-(5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-pyrrolidine-2-carboxylic acid amide;
(S)-1-(5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-pyrrolidine-2-carboxylic acid amide;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-(((2-methanesulphonyl-ethyl)-methyl-amino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
N-(2-((5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-amino)-ethyl)-methanesulphonamide;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

Further particularly preferred compounds of the present invention include:
1-(3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-1,2,4-oxadiazol-5-ylmethyl)-piperidin-4-one;
1-(3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-1,2,4-oxadiazol-5-ylmethyl)-pyrrolidin-2-one;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

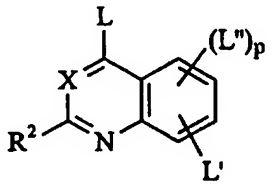
Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit *cis-trans* isomerism).

The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are included within the scope of the present invention. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen in the compound of formula (I). The therapeutic activity resides in the moiety derived from the compound of the invention as defined herein and the identity of the other component is of less importance although for therapeutic and prophylactic purposes it is, preferably, pharmaceutically acceptable to the patient. Examples of pharmaceutically acceptable acid addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acids, and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, glycollic, gluconic, succinic and methanesulphonic and arylsulphonic, for example *p*-toluenesulphonic, acids.

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) as defined above which comprises the steps:

(a) the reaction of a compound of formula (II)

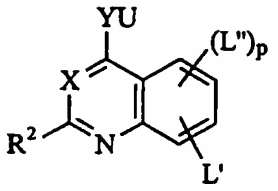


(II)

wherein X, p and R^2 are as defined above and L, L' and L" are suitable leaving groups, with a compound of formula (III)

UYH (III)

wherein U and Y are as defined above, to prepare a compound of formula (IV)

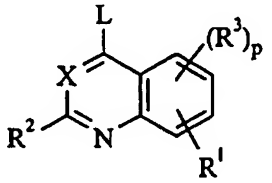


(IV)

and subsequently (b) reaction with an appropriate reagent to substitute the group R^1 onto the phenyl ring by replacement of the leaving group L'; and (c) where p is other than 0, reaction with appropriate reagent(s) to substitute the group(s) R^3 onto the phenyl ring by replacement of the leaving group(s) L"; and, if desired, (d) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

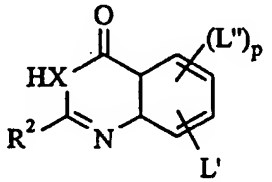
Alternatively, the compound of formula (II) as defined above is reacted with the appropriate reagents to substitute the groups R^1 and R^3 onto the phenyl ring by replacement of the respective leaving groups and then the product thereby obtained (of formula (V) below) is reacted with the compound of formula (III) as defined above, followed, if desired, by conversion of the compound of formula (I) thereby obtained into another compound of formula (I).

In a variant of this alternative the compound of formula (V)



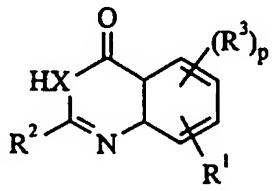
(V)

may be prepared by the reaction of a compound of formula (VI)



(VI)

with appropriate reagents to substitute the group(s) R^3 and the group R^1 onto the phenyl ring to prepare a compound of formula (VII)



(VII)

and subsequent reaction to incorporate the leaving group L. For example, a chloro leaving group can be incorporated by reaction of a corresponding 3,4-dihydropyrimidone with carbon tetrachloride/triphenylphosphine in an appropriate solvent.

Simplified versions of these general processes will apply where p is 0.

The group R^1 may, therefore, be substituted onto the phenyl ring by replacement of a suitable leaving group. This is especially suitable for preparing compounds where R^1 is a substituted or unsubstituted phenyl or heterocyclic ring system; such compounds may, for example, be prepared by reaction of the corresponding aryl or heteroaryl stannane derivative with the corresponding compound of formula (IV) carrying the leaving group L' in the appropriate position on the ring.

The group(s) R^3 may, therefore, also be substituted onto the phenyl ring by replacement of suitable leaving group(s). This is especially suitable for preparing compounds of formula (I) wherein an R^3 group is linked to the phenyl ring by a nitrogen atom; such compounds may, for example, be obtained by reaction of the amine corresponding to the group R^3 with the corresponding compound carrying a halo substituent in the appropriate position on the ring.

The reagents used to effect the substitution of the groups R^1 and R^3 onto the phenyl ring may, in certain circumstances, include appropriate protecting group(s) well known to the person skilled in the art for particular functionalities. This may, for example, be suitable where either of the groups R^1 or R^3 contain a free amino functionality. Such protecting group(s) would be removed by standard methods after

the substitution onto the phenyl ring has been effected. For a description of protecting groups and their use see T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd edn., John Wiley & Sons, New York, 1991.

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) as defined above which comprises the steps:

(a) reacting a compound of formula (IV) as defined above with appropriate reagent(s) to prepare a compound wherein either the group L' or the group(s) L" (when p is other than 0) is(are) replaced with an appropriately functionalised group Z;

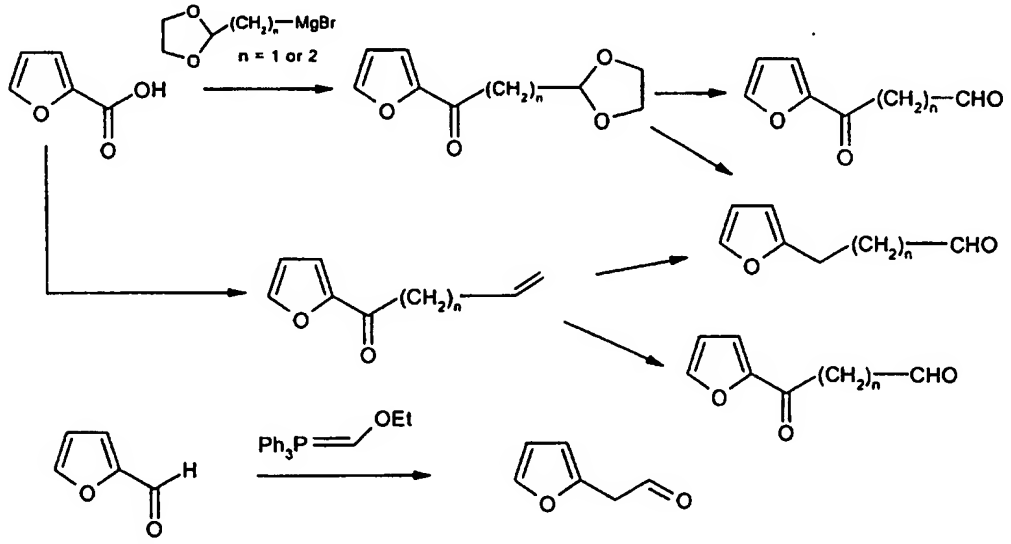
and (b) subsequently converting the group Z into the group R^1 where L' has been replaced or into the group R^3 where L" has been replaced by means of appropriate reagent(s); (c) reacting with appropriate reagents to substitute the other of R^3 and R^1 onto the phenyl ring by replacement of the remaining leaving group L" and L' respectively, if present; and, if desired, (d) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

Such processes are particularly suitable for the preparation of compounds of formula (I) wherein either R^1 carries or R^3 represents a substituent selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined above in which M^2 represents NR^{12}. In such cases preferably the group Z carries a terminal formyl group (CHO).

Such processes are especially suitable for the preparation of compounds of formula (I) wherein p is 0 and R^1 carries a substituent selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined above in which M^2 represents NR^{12}.

Where Z carries a formyl group the compound may be suitably prepared from the corresponding dioxolanyl substituted compound, for example by acid hydrolysis. The dioxolanyl substituted compound may be prepared by reaction of a compound of formula (IV) with an appropriate reagent to substitute the relevant leaving group with the substituent carrying the dioxolanyl ring. This reagent could, for example, be an appropriate heteroaryl stannane derivative.

Where Z carries a terminal formyl group the compound could suitably be prepared by reaction of a compound of formula (IV) with an appropriate heteroaryl stannane derivative. This derivative is either readily available or can be readily synthesised by those skilled in the art using conventional methods of organic synthesis. Suitable possibilities for preparation of compounds where R^1 carries the aforementioned substituents include the following schematic examples:-



The resulting compounds would, for example, then be converted into the respective stannane derivative.

Analogous methods could be used for phenyl and other heterocyclic ring systems and also for the preparation of compounds where R^3 represents one of the aforementioned substituents.

Therefore a suitable process may comprise reaction of the compound in which the group Z carries a terminal formyl group (i.e. a -CHO or -(C_{1-3} alkylene)-CHO group) with a compound of formula HM^2-M^3-M^4, a compound of formula HM^2-$M^{3'}$-M^6 or a compound of formula HM^5, wherein M^2 represents NR^{12}. The reaction preferably involves a reductive amination by means of an appropriate reducing agent, for example sodium triacetoxyborohydride.

A similar process would be involved where in M^1 one CH_2 group was replaced with a CO group and M^2 was NR^{12}. If necessary, in certain circumstances, the ketone could be protected by standard methods to ensure that the reductive amination involved the aldehyde functionality.

For the preparation of those compounds wherein in M^1 the CH_2 group adjacent to M^2 is replaced with a CO group a suitable process would comprise reaction of a compound in which the group Z carries a -(C_{0-3} alkylene)-CO_2H group with a compound of formula HM^2-M^3-M^4, a compound of formula HM^2-$M^{3'}$-M^6 or a compound of formula HM^5, wherein M^2 represents NR^{12}.

Alternatively, an analogous scheme to those described above could be used wherein the substitution of the groups R^1 and R^3 onto the phenyl ring occurs prior to the coupling reaction with the compound of formula (III).

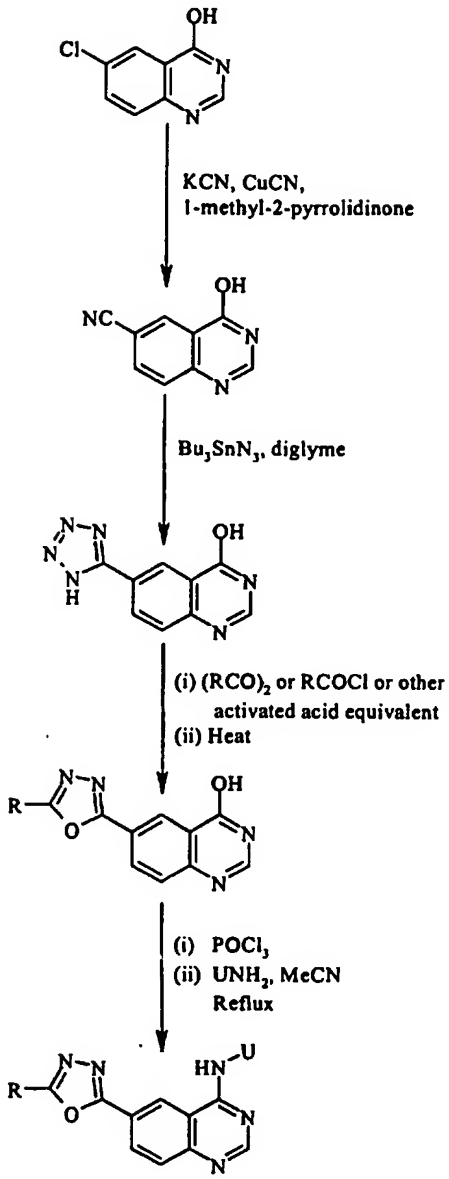
According to a further alternative process the group Z is converted into the group R^1 by a *de novo* synthesis of a substituted or unsubstituted heterocyclic ring system using appropriate reagents. Such a process would involve standard synthetic methodology known to the person skilled in the art for building up the heterocyclic ring system.

For example, Z could suitably represent an alkyne group which when reacted with an appropriate nitrile oxide results in the formation of an isoxazole ring system; reaction with an azide would result in the formation of a triazole ring system. The group Z could also suitably represent an amidoxime group (derived from a cyano group) which when reacted with an activated carboxylic acid derivative (such as an acid chloride or an acid imidazolide) would result in the formation of a 1,2,4-oxadiazole ring system. The group Z could also suitably represent a bromomethylenecarbonyl group which would be reacted with an imidate to result in the formation of an oxazole ring system, with a guanidino group to result in the formation of an N-imidazole ring system or with an amidine group to result in the formation of a C-imidazole ring system. The group Z could also suitably represent an activated carboxylic acid group which would be reacted to form a hydrazinoketone which would subsequently be reacted with another activated carboxylic acid derivative to result in the preparation of a 1,3,4-oxadiazole ring

system. Thus reaction of a compound carrying a relevant Z group with appropriate reagents carrying one of
-C=N=O, -NH-C(NH_2)=NH, -COX, -C(NH_2)=NOH, -C(OMe)=NH, or
-C(NH_2)=NH as a terminal group would result in the formation of the ring systems indicated above.

Alternatively, an analogous scheme to those described above could be used wherein the substitution of the group R^1 onto the phenyl ring occurs prior to the coupling reaction with the compound of formula (III).

The following scheme outlines, for example, the synthesis of derivatives carrying a substituted 1,3,4-oxadiazole ring as an R^1 substituent:



Such processes are particularly suitable for the preparation of the compounds of formula (I) wherein R^1 carries a substituent selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined above in which M^2 represents $CR^{12}R^{13}$, including those in which in M^1 one CH_2 group is replaced by a CO group.

Such processes are especially suitable for the preparation of compounds of formula (I) wherein p is 0 and R^1 carries a substituent selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined above in which M^2 represents $CR^{12}R^{13}$.

Suitable leaving groups for L, L' and L" will be well known to those skilled in the art and include, for example, halo such as chloro and bromo; sulphonyloxy groups such as methanesulphonyloxy and toluene-p-sulphonyloxy; alkoxy groups; and triflate.

The coupling reaction referred to above with the compound of formula (III) is conveniently carried out in the presence of a suitable inert solvent, for example a C_{1-4} alkanol, such as isopropanol, a halogenated hydrocarbon, an ether, an aromatic hydrocarbon or a dipolar aprotic solvent such as acetone or acetonitrile at a non-extreme temperature, for example from 0 to 150°, suitably 10 to 100°C, preferably 50 to 100°C.

Optionally, the reaction is carried out in the presence of a base when Y = NH. Examples of suitable bases include an organic amine such as triethylamine, or an alkaline earth metal carbonate, hydride or hydroxide, such as sodium or potassium carbonate, hydride or hydroxide. When YH = OH or SH it is necessary to perform the reaction in the presence of a base, and in such a case the product is not obtained as the salt.

The compound of formula (I) in the case in which Y = NR^b may be obtained from this process in the form of a salt with the acid HL, wherein L is as hereinbefore defined, or as the free base by treating the salt with a base as hereinbefore defined.

The compounds of formulae (II) and (III) as defined above, the reagents to substitute the group(s) R^3 and the group R^1, and the reagent(s) to convert the group Z into the group R^3 or R^1 are either readily available or can be readily synthesised by those skilled in the art using conventional methods of organic synthesis.

As indicated above, the compound of formula (I) prepared may be converted to another compound of formula (I) by chemical transformation of the appropriate substituent or substituents using appropriate chemical methods (see for example, J.March "Advanced Organic Chemistry", Edition III, Wiley Interscience, 1985).

For example, a group R^3 may be substituted onto the phenyl ring by replacement of another group R^3 which is a suitable leaving group. This is especially suitable for preparing compounds of formula (I) wherein an R^3 group is linked to the phenyl ring by a nitrogen atom; such compounds may, for example, be obtained by reaction of the amine corresponding to the group R^3 with the corresponding compound of formula (I) carrying a halo substituent in the appropriate position on the ring.

Similarly a group R^1 may be substituted onto the phenyl ring by replacement of a group R^3 which is a suitable leaving group. This is especially suitable for preparing compounds where R^1 is a phenyl or heterocyclic ring system; such compounds may, for example, be prepared by reaction of the corresponding aryl or heteroaryl stannane derivative with the corresponding compound of formula (I) carrying a halo substituent in the appropriate position on the ring.

For example, a compound containing an alkyl or aryl mercapto group may be oxidised to the corresponding sulphinyl or sulphonyl compound by use of an organic peroxide (eg benzoyl peroxide) or suitable inorganic oxidant (eg OXONE ®).

A compound containing a nitro substituent may be reduced to the corresponding amino-compound, eg by use of hydrogen and an appropriate catalyst (if there are no other susceptible groups) or by use of Raney Nickel and hydrazine hydrate.

Amino or hydroxy substituents may be acylated by use of an acid chloride or an anhydride under appropriate conditions. Equally an acetate or amide group may be cleaved to the hydroxy or amino compound respectively by treatment with, for example, dilute aqueous base.

In addition reaction of an amino substituent with triphosgene and another amine (eg aqueous ammonia, dimethylamine) gives the urea substituted product.

An amino substituent may also be converted to a dimethylamino substituent by reaction with formic acid and sodium cyanoborohydride.

A formyl substituent may be converted to a hydroxymethyl or a carboxy substituent by standard reduction or oxidation methods respectively.

All of the above-mentioned chemical transformations may also be used to convert one compound of formula (II) to a further compound of formula (II) prior to any subsequent reaction; or to convert one compound of formula (II) to a further compound of formula (III) prior to any subsequent reaction.

Various intermediate compounds used in the above-mentioned processes, including but not limited to certain of the compounds of formulae (II), (III), (IV), (V), (VI) and (VII) as illustrated above, are novel and thus represent a further aspect of the present invention.

The compounds of formula (I) and salts thereof have anticancer activity as demonstrated hereinafter by their inhibition of the protein tyrosine kinase c-erbB-2, c-erbB-4 and/or EGF-r enzymes and their effect on selected cell lines whose growth is dependent on c-erbB-2 or EGF-r tyrosine kinase activity.

The present invention thus also provides compounds of formula (I) and pharmaceutically acceptable salts or solvates thereof for use in medical therapy, and particularly in the treatment of disorders mediated by aberrant protein tyrosine kinase activity such as human malignancies and the other disorders mentioned above. The compounds of the present invention are especially useful for the treatment of disorders caused by aberrant c-erbB-2 and/or EGF-r activity such as breast, ovarian, gastric, pancreatic, non-small cell lung, bladder, head and neck cancers, and psoriasis.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from a disorder mediated by aberrant protein tyrosine kinase activity, including susceptible malignancies, which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in therapy.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of cancer and malignant tumours.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of psoriasis.

Whilst it is possible for the compounds or salts of the present invention to be administered as the new chemical, it is preferred to present them in the form of a pharmaceutical formulation.

According to a further feature of the present invention there is provided a pharmaceutical formulation comprising at least one compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain for example 0.5mg to 1g, preferably 70mg to 700mg, more preferably 5mg to 100mg of a compound of the formula (I) depending on the condition being treated, the route of administration and the age, weight and condition of the patient.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The animal requiring treatment with a compound, salt or solvate of the present invention is usually a mammal, such as a human being.

A therapeutically effective amount of a compound, salt or solvate of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. However, an effective amount of a compound of the present invention for the treatment of neoplastic

growth, for example colon or breast carcinoma will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt or solvate of the present invention may be determined as a proportion of the effective amount of the compound per se.

The compounds of the present invention and their salts and solvates may be employed alone or in combination with other therapeutic agents for the treatment of the above-mentioned conditions. In particular, in anti-cancer therapy, combination with other chemotherapeutic, hormonal or antibody agents is envisaged. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one other pharmaceutically active agent. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Certain embodiments of the present invention will now be illustrated by way of example only. The physical data given for the compounds exemplified is consistent with the assigned structure of those compounds.

^{1}H NMR spectra were obtained at 250MHz on a Bruker AC250 or Bruker AM250 spectrophotometer. J values are given in Hz. Mass spectra were obtained on one of the following machines: VG Micromass Platform (electrospray positive or negative) or HP5989A Engine (thermospray positive). Analytical thin layer chromatography (tlc) was used to verify the purity of some intermediates which could not be isolated or which were too unstable for full characterisation, and to follow the progress of reactions. Unless otherwise stated, this was done using silica gel (Merck Silica Gel 60 F254). Unless otherwise stated, column chromatography for

the purification of some compounds used Merck Silica gel 60 (Art. 1.09385, 230-400 mesh), and the stated solvent system under pressure.
Petrol refers to petroleum ether, either the fraction boiling at 40-60°C, or at 60-80°C.
Ether refers to diethylether.
DMAP refers to 4-dimethylaminopyridine.
DMF refers to dimethylformamide.
DMSO refers to dimethylsulphoxide.
IMS refers to industrial methylated spirit.
THF refers to tetrahydrofuran.
TMEDA refers to *N,N,N',N'*-tetramethylethylenediamine.
HPLC refers to high pressure liquid chromatography.
RT refers to retention time.

Useful preparative techniques are described in WO96/09294, WO97/03069 and WO97/13771; also described in these publications are appropriate intermediate compounds other than those detailed below.

General Procedures

(A) Reaction of an amine with a quinazoline or quinoline

The optionally substituted quinazoline or quinoline and the specified amine were mixed in an appropriate solvent and heated to reflux. When the reaction was complete (as judged by tlc), the reaction mixture was allowed to cool. The resulting suspension was diluted, *e.g.* with acetone, and the solid collected by filtration, washing *e.g.* with excess acetone, and dried at 60°C *in vacuo*, giving the product as the hydrochloride salt. If the free base was required (*e.g.* for further reaction), this was obtained by treatment with a base *e.g.* triethylamine; purification by chromatography was then performed, if required.

(B) Reaction of a product from Procedure (A) with a heteroaryl tin reagent

A stirred mixture of the product from Procedure (A), (containing a suitable leaving group such as chloro, bromo, iodo or triflate), a heteroaryl stannane and a suitable palladium catalyst, such as bis-(triphenylphosphine)palladium (II) chloride or 1,4-bis(diphenylphosphino)-butane palladium (II) chloride (prepared as described in C.E.Housecroft et. al, Inorg. Chem. (1991), 30(1), 125-30), together with other appropriate additives, were heated at reflux in dry dioxane or

another suitable solvent under nitrogen until the reaction was complete. The resulting mixture was generally purified by chromatography on silica.

(C) Preparation of 6-(5-substituted-1,2,4-oxadiazol-3-yl)quinazolines

Powdered molecular sieves (0.025g) were added to a solution of a 4-substituted-quinazolin-6-yl-(*N*-hydroxycarboximidamide) (0.20mmol) in dry THF (10ml), and the mixture was stirred at room temperature for 15 minutes. Sodium hydride (0.008g of 60% dispersion in mineral oil, 0.20mmol) was added and stirring continued for 30 minutes. An appropriate ester (0.20mmol or more) was added and the mixture was heated to reflux for several hours. The reaction mixture was concentrated *in vacuo*, and purified by chromatography on silica using a Bond Elut ™ cartridge, using appropriate solvents for elution.

Preparation of Intermediates

4-Benzyloxyaniline is commercially available as the hydrochloride salt; this is treated with aqueous sodium carbonate solution, and the mixture extracted with ethyl acetate; the organic solution is dried ($MgSO_4$) and concentrated to give the free base as a brown solid, used without further purification.

Other substituted anilines were in general prepared by analogous methods to those outlined in WO 96/09294 and/or as follows:

Step 1: Preparation of the precursor nitro-compounds

4-Nitrophenol (or an appropriate substituted analogue, such as 3-chloro-4-nitrophenol) was treated with a base such as potassium carbonate or sodium hydroxide in an appropriate solvent, such as acetone or acetonitrile. The appropriate aryl or heteroaryl halide was added and the reaction mixture heated or stirred at room temperature overnight.

Purification A: Most of the acetonitrile was removed *in vacuo*, and the residue was partitioned between water and dichloromethane. The aqueous layer was extracted with further dichloromethane (x 2), and the combined dichloromethane layers were concentrated *in vacuo*.

Purification B: removal of insoluble material by filtration, followed by concentration of the reaction mixture *in vacuo*, and chromatography on silica.

Step 2: Reduction to the corresponding aniline

The precursor nitro compound was reduced by catalytic hydrogenation at atmospheric pressure using 5%Pt/carbon, in a suitable solvent (e.g. ethanol, THF, or mixtures thereof to promote solubility). When reduction was complete, the mixture was filtered through Harborlite™, washing with excess solvent, and the resulting solution concentrated *in vacuo* to give the desired aniline. In some cases, the anilines were acidified with HCl (e.g. in a solution in dioxane) to give the corresponding hydrochloride salt.

Anilines prepared by such methods include:
4-(2-Fluorobenzyloxy)aniline; m/z $(M+1)^+$ 218
4-(3-Fluorobenzyloxy)aniline; m/z $(M+1)^+$ 218
4-(4-Fluorobenzyloxy)aniline; m/z $(M+1)^+$ 218
3-Chloro-4-(2-fluorobenzyloxy)aniline; m/z $(M+1)^+$ 252
3-Chloro-4-(3-fluorobenzyloxy)aniline; m/z $(M+1)^+$ 252
3-Chloro-4-(4-fluorobenzyloxy)aniline; m/z $(M+1)^+$ 252
4-(Pyridyl-2-methoxy)aniline; m/z $(M+1)^+$ 201
4-(Pyridyl-4-methoxy)aniline; m/z $(M+1)^+$ 201
4-(Pyridyl-3-methoxy)aniline; m/z $(M+1)^+$ 201
4-Benzyloxy-3-chloroaniline; m/z $(M+1)^+$ 234
and, in appropriate cases, their hydrochloride salts.

4-Benzenesulphonylaniline was prepared by the published method (Helv. Chim. Acta., 1983, 66(4), p1046.

1-Benzyl-5-nitro-1H-indole

Dry dimethylsulphoxide (20 ml) was added to potassium hydroxide (4.2 g, 0.074 mol) (crushed pellets) and the mixture was stirred under nitrogen for 5 mins. 5-Nitroindole (commercially available) (3.0 g, 0.019 mol) was then added and the red mixture stirred for 30 min at room temperature. The mixture was then cooled to -10 °C, benzyl bromide (4.4 ml, 0.037 mol) was slowly added and the mixture stirred and allowed to warm to room temperature over a period of 40 mins.

Water (50 ml) was then added and the mixture was extracted with diethyl ether (2 x 200 ml). The extracts were washed with water (4 x 50 ml), dried over sodium sulphate and evaporated to leave an oily solid. The excess benzyl bromide was removed by dissolving the whole in diethyl ether (50 ml), diluting this solution with 40-60 petrol (50 ml) and then gradually removing the diethyl ether *in vacuo* to leave a yellow solid suspended in the petrol. The solid was filtered, washed with copious amounts of 40-60 petrol and dried to give 1-benzyl-5-nitroindole (2.4 g, 51%) as a yellow solid, m.p. 102-104 °C; δH [$^2H_6$]-DMSO 8.53 (1H, s, 4-H), 8.00 (1H, d, J 9, 6-H), 7.78 (1H, s, 2-H), 7.68 (1H, d, J 9, 7-H), 7.36-7.20 (5H, m, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H), 6.81 (1H, s, 3-H), 5.52 (2H, s, CH_2).

5-Amino-1-benzyl-1H-indole

A solution of 1-benzyl-5-nitroindole (0.51 g, 0.02 mol) in a mixture of ethyl acetate (25 ml) and methanol (25 ml) was carefully added to 10% palladium on charcoal (45 mg). The resulting suspension was stirred at room temperature under an atmosphere of hydrogen. When the reaction was complete (indicated by tlc or calculated uptake of hydrogen) the suspension was filtered through a pad of Harbolite™, and the filtrate evaporated to dryness to give 5-amino-1-benzylindole (0.40 g, 91%) as an off-white solid; m.p. 66-68 °C; δH [$^2H_6$]-DMSO 7.30-7.12 (6H, m, 2-H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H), 7.08 (1H, d, J 8, 7-H), 6.70 (1H, s, 4-H), 6.49 (1H, d, J 8, 6-H), 6.18 (1H, s, 3-H), 5.28 (2H, s, CH_2), 4.38 (2H, br s, NH_2).

2-Benzyl-5-nitro-1H-benzimidazole

A mixture of 4-nitro-o-phenylene diamine (1.54g) and phenylacetic acid (2.04g) in 5N aqueous HCl (16ml) were heated at 110 °C under nitrogen for 22 hours. The mixture was cooled to room temperature and the accumulated black solid collected by filtration. This crude residue was then adsorbed onto silica and chromatographed to give the title compound (0.84g) as a purple foam; δH $CDCl_3$ 9.70 (1H, bs), 8.15 (1H, d), 7.30 (7H, m), 4.30 (2H,s); m/z $(M + 1)^+$ 254.

5-Amino-2-benzyl-1H-benzimidazole

The title compound was prepared from 5-nitro-2-benzylbenzimidazole by an analogous reduction method to that described above for 5-amino-1-benzyl-1H-indole; m/z $(M + 1)^+$ 224. Also note the published method (J. Het. Chem., 23, 1109-13, (1986)).

1-*N*-Benzyl-5-nitro-1H-indazole and 2-*N*-Benzyl-5-nitro-1H-indazole

A stirred mixture of 5-nitroindazole (50g), potassium carbonate (46.6g, 1.1 equiv.) and benzyl bromide (57.6g, 1.1 equiv) in *N,N*-dimethylformamide (500 ml) was heated at 75°C for a period of 4 hours. The reaction was then cooled and water (500ml) was gradually added to precipitate the product which was filtered off and washed with water (50ml) and dried in the air at ambient temperature. The weight of pale yellow solid thus obtained was 72.3g (93%), m.pt. 95-97°C; HPLC (Partisil 5, dichloromethane, 4ml/min, 250nm) gave an isomer ratio (1-*N*-benzyl : 2-*N*-benzyl) of 63:37 (RT-1*N* 3.4min, RT-2*N* 6.6min). To a filtered solution of the mixed regioisomers (100g) in acetone (470ml) at room temperature was added, gradually with stirring, water (156ml) and the mixture was stirred for one hour. The resultant yellow crystalline solid was filtered off and dried in the air at ambient temperature to give 36.4g (34%) of material; m.pt.124-126°C; HPLC showed an isomer ratio (1-*N*-benzyl : 2-*N*-benzyl) of 96:4; δH ($CDCl_3$) 5.58 (2H,s,CH_2), 7.12-7.15(2H) & 7.22-7.29(3H)-(phenyl), 7.33(1H,dt, J=1Hz & 9Hz, H-7), 8.15(1H,dd, J=2Hz & 9Hz,H-6), 8.19(1H,d,J=1Hz,H-3), 8.67 (1H,dd,J=1Hz & 2Hz, H-4).

Also note the published method in FR 5600, 8 January 1968.

5-Amino-1-*N*-benzyl-1H-indazole

1-Benzyl-5-nitroindazole (400g) was suspended in ethanol (5 litre) and hydrogenated in the presence of 5% platinum on carbon catalyst (20g) operating at 1 bar pressure and 50-60°C. When hydrogen uptake was complete the reactor contents were heated to 70°C, discharged and filtered while still hot and the filtrate concentrated to ~4 litre which caused some crystallisation. Water (4 litre) was then gradually added with stirring and the mixture was stirred at 5°C overnight. The resultant crystals were filtered off and air-dried at ambient temperature to give 305g (86%) of material, m.pt.150-152°C; HPLC (Supelcosil ABZ +, gradient 0.05% trifluoroacetic acid in water/0.05% trifluoroacetic acid in acetonitrile,1.5ml/min, 220nm) showed <1% of the corresponding 2-*N*-isomer

(RT-1*N* 6.03min, RT-2*N* 5.29min); δH ($CDCl_3$) 3.3-3.8(2H,broad s,NH_2), 5.47 (2H,s,CH_2), 6.74(1H,dd,J=2Hz & 9Hz,H-6), 6.87(1H,dd,J=1Hz & 2Hz,H-4), 7.06-7.11(3H) & 7.17-7.25(3H)-(phenyl & H-7), 7.77(1H,d,J=1Hz,H-3).

Also note the published method in FR 5600, 8 January 1968.

1-Benzyl-3-methyl-5-nitro-1H-indazole

2-Fluoro-5-nitroacetophenone (H. Sato et al, Bioorganic and Medicinal Chemistry Letters, 5(3), 233-236, 1995) (0.24g) was treated with triethylamine (0.73ml)and benzyl hydrazine dihydrochloride (0.255g) in ethanol (20ml) at reflux under N_2 for 8 days. The mixture was cooled and the solid 1-benzyl-3-methyl-5-nitroindazole (0.16g) was collected by filtration; m/z $(M+1)^+$ 268.

1-Benzyl-3-methyl-1H-indazol-5-ylamine

1-Benzyl-3-methyl-5-nitroindazole (0.15g) in THF (15ml) was treated with platinum on carbon (0.05g, 5%) under an atmosphere of hydrogen at room temperature. When hydrogen uptake was complete, the mixture was filtered and concentrated *in vacuo* to give the title compound; m/z $(M+1)^+$ 268.

Further amino-indazole intermediates

The relevant nitro-substituted 1H-indazole was treated with a base such as potassium carbonate or sodium hydroxide in a suitable solvent, such as acetone or acetonitrile. The appropriate aryl halide or heteroaryl halide was added and the reaction mixture heated or stirred at room temperature overnight. Subsequent concentration *in vacuo* and chromatography on silica gave the desired 1-substituted nitro-1H-indazoles. Hydrogenation was carried out by analogy with the preparation of 5-amino-1-benzyl-1H-indole described above.

Amines prepared by such methods include:-

5-Amino-1-benzyl-1H-indazole; m/z $(M+1)^+$ 224
5-Amino-1-(2-fluorobenzyl)-1H-indazole; m/z $(M+1)^+$ 242
5-Amino-1-(3-fluorobenzyl)-1H-indazole; m/z $(M+1)^+$ 242
5-Amino-1-(4-fluorobenzyl)-1H-indazole; m/z $(M+1)^+$ 242
5-Amino-1-(2-pyridylmethyl)-1H-indazole; m/z $(M+1)^+$ 225
5-Amino-1-(3-pyridylmethyl)-1H-indazole; m/z $(M+1)^+$ 225

5-Amino-1-(4-pyridylmethyl)-1H-indazole; m/z $(M+1)^+$ 225
5-Amino-1-(2,3-difluorobenzyl)-1H-indazole; m/z $(M+1)^+$ 260
5-Amino-1-(3,5-difluorobenzyl)-1H-indazole; m/z $(M+1)^+$ 260.

1-Benzenesulphonylindol-5-yl-amine was prepared according to the published method (J. Org. Chem., 55, 1379-90, (1990)).

3-Benzenesulphonylindol-6-yl-amine
3-Benzenesulphonyl-6-nitroindole (K. Wojciechowski and M Makosza, Tet. Lett., 25 (42), p4793, 1984) was hydrogenated by analogy with the procedures above to give the title compound; δH $[^2H_6]$DMSO 11.64 (1H,s), 7.94 (2H,m), 7.81 (1H,s), 7.57 (3H,m), 7.49(1H,d), 6.60(1H,s), 6.55 (1H,dd), 5.40 (2H,s).

4-Chloro-6-bromoquinazoline and 4-Chloro-6-iodoquinazoline were prepared as described in WO 96/09294.

(4-Benzyloxy-phenyl)-(6-bromoquinazolin-4-yl)-amine hydrochloride
4-Chloro-6-bromoquinazoline (0.25g, 1.0mmol) and 4-benzyloxyaniline (0.25g, 1.3mmol) were mixed in 2-propanol (6ml) and heated at reflux for 10 mins (Procedure A). The solution was allowed to cool at room temperature and the 2-propanol removed *in vacuo*. The resulting solid was triturated with acetone to give the product as a yellow solid (0.39g, 88%); δH $[^2H_6]$-DMSO 11.60 (1H, b, NH), 9.21 (1H, s, 5-H), 8.86 (1H, s, 2-H), 8.20 (1H, d, 7-H), 7.90 (1H, d, 8-H), 7.65 (2H, d, 2'-H, 6'-H), 7.50-7.25 (5H, m, Ph-H), 7.10 (2H, d, 3'-H, 5'-H), 5.15 (2H, s, CH_2); m/z 405/407 (M+).

(1-Benzyl-1H-indazol-5-yl)-(6-bromoquinazolin-4-yl)-amine (Procedure A)
6-Bromo-4-chloroquinazoline (5.0g) was reacted with 5-amino-1-benzyl-1H-indazole (5.0g) in acetonitrile (100ml) at 100°C. The resulting precipitate was treated with triethylamine in ethyl acetate and water to give the title compound as a yellow solid, (7.37g); δH $[^2H_6]$ -DMSO 9.93(1H,s), 8.82 (1H,d), 8.52(1H,s), 8.19(1H,s), 8.09(1H,s), 7.92(1H,dd), 7.65(3H,m), 7.25(5H,m), 5.62(2H,s).

(1-Benzyl-1H-indazol-5-yl)-(6-iodoquinazolin-4-yl)-amine hydrochloride

4-Chloro-6-iodoquinazoline (5.8g) was treated with 5-amino-1-benzyl-1H-indazole (3.90g) in acetonitrile (500ml) at reflux under N_2 for 18 hours (Procedure A). Subsequent cooling and filtration gave the title compound (8.26g); m/z $(M+1)^+$ 478.

4-Nitro-1,3-dibenzoic acid

4-Nitro-m-xylene (27.0g, 178.6mmol) was added to water (1.20 l) and heated to reflux. Potassium permanganate (174g, 1101mmol) was added portionwise over 6 hours. The reaction was allowed to cool and left to stand for three days. It was then reheated and filtered while hot. The filtrate was cooled (ice bath), and acidified with conc. HCl. After standing for 2 hours, the resulting cream precipitate was collected by filtration to give the title compound (21.5g, 101.8mmol, 57%); δH [$^2H_6$] DMSO 13.0 (2H,br s), 8.33 (1H,s), 8.36 (1H,d), 8.27 (1H,d).

4-Amino-1,3-dibenzoic acid

A solution of 4-nitro-1,3-dibenzoic acid (21.5g,101.8mmol) in ethanol (540ml) was reduced using hydrogen at atmospheric pressure and catalytic palladium/carbon (2.0g, 10%Pd/C on dry weight, 50% water). The mixture was diluted with DMF to dissolve the product and filtered through Harbolite™. Concentration of the filtrate *in vacuo* gave a white solid which was washed with water and dried at 60°C *in vacuo* to give the title compound (17.77g, 98.1mmol, 96%); δH [$^2H_6$] DMSO 12.5 (2H,br s), 8.35 (1H,d), 7.73 (1H,dd), 6.77 (1H,d).

6-(Carboxy)-quinazolin-4-one

4-Amino-1,3-dibenzoic acid (6.9g) was treated with formamide (14ml) at 180°C under N_2. After 3.5 hours, the mixture was cooled and diluted with acetone (100ml). Filtration gave the title compound (4g) as a white solid; δH [$^2H_6$]DMSO 8.74(1H,d), 8.35 (1H,dd), 8.23 (1H,s), 7.72 (1H,d).

6-(Hydrazido)quinazolin-4-one

6-(Carboxy)quinazolin-4-one (4.84g) was treated with 1,1'-carbonyldiimidazole (8.28g) in THF at room temperature under N_2. After 8 hours, hydrazine hydrate (1.6ml) was added and stirring was continued for a further 16 hours. The resulting solid was filtered, washed with THF and dried *in vacuo* to yield the title compound

(4.66g) as a cream solid; δH [$^2H_6$]DMSO 10.1 (1H,bs), 8.60(1H,s), 8.70 (1H,m), 7.70 (1H,d), 7.02 (1H,s); m/z ($M+1^+$) 205.

6-(5-Methyl-1,3,4-oxadiazol-2-yl)quinazolin-4-one

6-(Hydrazido)quinazolin-4-one (3.00g) in triethylorthoacetate (100ml) was heated at reflux under N_2 for 5 hours. The cooled mixture was filtered to give the title compound as a cream solid; δH [$^2H_6$]DMSO 12.65 (1H,bs), 8.71(1H,d), 8.45 (1H,dd), 8.33 (1H,s), 7.95 (1H,s) 2.73 (3H,s); m/z ($M+1^+$) 229.

4-Chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)quinazoline

6-(5-Methyl-1,3,4-oxadiazol-2-yl)quinazolin-4-one (0.3g) was treated with phosphorus oxychloride at reflux under N_2 for 5 hours. The mixture was concentrated *in vacuo* and the residue azeotroped with toluene. This was then taken up in ethyl acetate and washed with 5% sodium bicarbonate and saturated brine, dried over magnesium sulphate and concentrated *in vacuo* to give the title compound (0.22g) as a yellow solid; δH [$^2H_6$]DMSO 12.65 (1H,bs), 8.71(1H,d), 8.45 (1H,dd), 8.33 (1H,s), 7.95 (1H,s) 2.73 (3H,s).

6-Cyanoquinazolin-4-one

6-Iodoquinazolin-4-one (10g) in 1-methyl-2-pyrrolidinone (50ml) was treated with copper (I) cyanide (4.28g) at 206°C under N_2 for 16 hours. The resulting mixture was cooled to 170°C and the methyl-2-pyrrolidinone removed by vacuum distillation. Potassium cyanide (2.4g) in water (30ml) and ethyl acetate (150ml) were added to the cooled residue and heating continued at 110°C for 1.5 hours. This mixture was then filtered hot through a pad of celite and the filter cake washed thoroughly with ethyl acetate. Subsequent separation, drying and concentration *in vacuo* gave the title compound (2.29g) as a beige solid; δH [$^2H_6$]DMSO 12.65(1H,bs), 8.53(1H,d), 8.28(1H,s), 8.19(1H,dd), 7.82(1H,d); m/z ($M-1^+$) 171.

An alternative synthetic method to prepare this compound is illustrated below.

6-(1,2,3,4-Tetrazol-5-yl)-quinazolin-4-one

6-Cyanoquinazolin-4-one (0.5g) in dimethylformamide (5ml) was treated with ammonium chloride (0.33g) and sodium azide (0.38g) and heated at 100°C under

nitrogen for 45 minutes. The resulting mixture was cooled, diluted with ethyl acetate and filtered. The filter cake was washed with dimethylformamide and ethyl acetate to give the title compound (0.56g) as a cream solid; δH [$^2H_6$]DMSO 13.00(1H,bs), 8.70(1H,d), 8.40(1H,dd), 8.38(1H,bs), 8.05(1H,s), 7.68(1H,d); m/z ($M-1^+$) 213.

6-(5-Methyl-1,3,4-oxadiazol-2-yl)quinazolin-4-one

6-(1,2,3,4-Tetrazol-5-yl)-quinazolin-4-one (3.31g) was treated with acetic anhydride (115ml) at reflux under N_2 for 1 hour. The anhydride was removed *in vacuo*, the residue absorbed onto silica and purified by chromatography to give the title compound as a white solid (3.47g). The analytical data was consistent with that given earlier.

6-(5-Trifluoromethyl-1,3,4-oxadiazol-2-yl)quinazolin-4-one

6-(1,2,3,4-Tetrazol-5-yl)-quinazolin-4-one (1.0g) was treated with trifluoroacetic anhydride (50ml) at 50°C under N_2 for 5 hours. The anhydride was removed *in vacuo*, the residue absorbed onto silica and purified by chromatography to give the title compound as a white solid (0.79g); δH [$^2H_6$]DMSO 12.63(1H,bs), 8.71(1H,d), 8.45(1H,dd), 8.27(1H,s), 7.90(1H,d); m/z ($M-1^+$) 281.

4-Chloro-6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)quinazoline

6-(5-Trifluoromethyl-1,3,4-oxadiazol-2-yl)quinazolin-4-one (0.79g) was treated with phosphorus oxychloride (18ml) and triethylamine (8ml) at reflux under N_2 for 2 hours. The mixture was concentrated *in vacuo* and the residue azeotroped with toluene. This was then taken up in ethyl acetate and washed with 5% sodium bicarbonate and saturated brine, dried over magnesium sulphate and concentrated *in vacuo* to give the title compound (0.76g) as an orange solid; δH $CDCl_3$ 9.17(1H,s), 9.05 (1H,d), 8.69(1H,dd), 8.30(1H,d).

(4-Benzyloxy-phenyl)-(6-iodoquinazolin-4-yl)-amine hydrochloride

4-Chloro-6-iodoquinazoline (8g) was treated with 4-benzyloxyaniline (5.5g) in acetonitrile (500ml) at reflux under N_2 for 18 hours. Subsequent cooling and filtration gave the title compound (13.13g); m/z $(M+1)^+$ 454.

(4-Benzyloxy-phenyl)-(6-cyanoquinazolin-4-yl)-amine

(4-Benzyloxy-phenyl)-(6-iodoquinazolin-4-yl)-amine (1.2g) in dioxane (10ml) under N_2 was treated with tributyltin cyanide (0.79g) and catalytic quantities of 1.4-bis-(diphenylphosphino)-butane palladium (II) chloride and tetrakis (triphenylphosphine) palladium at reflux for 23 hours. The mixture was absorbed onto silica and chromatographed to give the title compound (0.65g); δH [$^2H_6$]DMSO 10.01(1H,s), 9.14(1H,s), 8.63(1H,s), 8.15(1H,d), 7.87(1H,d), 7.73(2H,d), 7.45(5H,m), 7.10(2H,d), 5.13(2H,s); m/z $(M+1)^+$ 353.

(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-carboxylic acid

(1-Benzyl-1H-indazol-5-yl)-(6-iodoquinazolin-4-yl)-amine (0.48g) in DMF under CO was treated with sodium formate (0.1g) and catalytic quantities of triphenyl phosphine and bistriphenylphosphine palladium (II) chloride at 110°C. The mixture was cooled, added to 5% sodium hydroxide and extracted with ethyl acetate. The aqueous phase was treated with 2N HCl and the precipitated solid filtered and dried to give the title compound (0.07g); δH [$^2H_6$]DMSO 13.35(1H,bs), 10.40(1H,s), 9.30(1H,s), 8.60(1H,s), 8.30(1H,d), 8.17(2H,d), 7.84(1H,d), 7.72(1H,s), 7.30(5H,m), 5.70(2H,s); m/z $(M+1)^+$ 396.

(1-Benzyl-1H-indazol-5-yl)-(6-hydrazidoquinazolin-4-yl)-amine

(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-carboxylic acid (0.15g) and carbonyl diimidazole (0.123g) in dry THF (10ml) was stirred at 20°C for 3 hours under N_2. Hydrazine hydrate (0.04ml) was added and the mixture stirred at 20°C for 18 hours. The mixture was concentrated *in vacuo* to give the title compound as a solid (0.28g) which was used in subsequent synthetic steps without further purification; tlc (silica, CH_2Cl_2:EtOH:NH_3 100:8:1) Rf 0.18; m/z $(M+1)^+$ 410.

(1-Benzyl-1H-indazol-5-yl)-(6-(methanesulphonylethanoylhydrazido)-quinazolin-4-yl)-amine

Methanesulphonyl acetic acid (0.067g) and carbonyl diimidazole (0.119g) were stirred in a THF/DMF mixture (10ml/1ml) under N_2 for 3 hours. (1-Benzyl-1H-indazol-5-yl)-(6-hydrazidoquinazolin-4-yl)-amine (0.10g) was added and the mixture stirred

at 20°C for 18 hours. The mixture was absorbed onto silica and chromatographed to give the title compound (0.06g); m/z $(M+1)^+$ 530.

(1-Benzyl-1H-indazol-5-yl)-(6-cyanoquinazolin-4-yl)-amine

(1-Benzyl-1H-indazol-5-yl)-(6-iodoquinazolin-4-yl)-amine (3.58g) in dioxane (30ml) under N_2 was treated with tributyltin cyanide (2.51g) and catalytic quantities of 1.4-bis-(diphenylphosphino)-butane palladium (II) chloride and tetrakis (triphenylphosphine) palladium at reflux for 5 days. The mixture was absorbed onto silica and chromatographed to give the title compound (1.25g); δH $[^2H_6]$DMSO 10.20(1H,s), 9.15(1H,s), 8.65(1H,s), 8.24(1H,s), 8.18(2H,m), 7.89(1H,s), 7.70(2H,m), 7.30(5H,m), 5.70(2H,s); m/z $(M+1)^+$ 377.

1-Methyl-5-(1,3-dioxolan-2-yl)-imidazole

1-Methyl-5-formyl imidazole (0.64g) was treated with ethylene glycol (0.3ml), p-toluenesulphonic acid monohydrate (0.0015g) and powdered 4A molecular seives under N_2 for 18 hours at reflux. Subsequent cooling and filtration was followed by washing of the organic phase with aqueous sodium carbonate solution (2N), drying and concentration to give the title compound; δH ($CDCl_3$) 7.43 (1H,s), 7.12 (1H,s), 5.91 (1H,s), 4.10(4H,m), 3.70(3H,s).

5-Cyano-3-methylthio-2-oxoindole

Sulphuryl chloride (3.4ml, 5.71g, 42.4mmol) was added via syringe to a stirred solution of ethyl 2-(methylthio)acetate (5.4ml, 5.63g, 42.0mmol) in dry dichloromethane (30ml) cooled to -78°C, under a nitrogen atmosphere. After stirring for 15 min, a solution of 4-cyanoaniline (5.0g, 42.3mmol) and 1,8-bis(dimethylamino) naphthalene (9.0g, 42.0mmol) in dry dichloromethane (50ml) was added maintaining the temperature at -78°C. Stirring was continued for 3 hours at -78°C, and then triethylamine (5.9ml, 4.28g, 42.3mmol) was added at -78°C, and then the mixture was allowed to warm to room temperature. Stirring was continued under a nitrogen atmosphere for 3 days. Glacial acetic acid (5.0ml, 5.25g, 87.3ml) was then added and the mixture was stirred for 1 hour. The reaction mixture was washed with 8%aq. $NaHCO_3$ (50ml) and water (2 x 100ml), dried (Na_2CO_3), and concentrated *in vacuo*. Silica gel chromatography, eluting with 1:2 ethyl acetate/*i*-hexane, gave 5-cyano-3-methylthio-2-oxoindole as a yellow solid (2.8g, 13.7mmol, 32%); δH $CDCl_3$ 8.95 (1H,br s), 7.67 (1H,s). 7.60 (1H,d), 7.01 (1H,d), 4.30 (1H,s), 2.08 (3H,s).

2-Amino-5-cyanobenzoic acid

Air was bubbled through a stirred solution of 5-cyano-3-methylthio-2-oxoindole (18.0g, 88.1mmol) and potassium hydroxide (5.9g, 105.2mmol) in a 9:1 mixture of methanol:water at room temperature for 5 hours. Further potassium hydroxide (5.9g, 105.2mmol) was added and the air bubbling continued overnight. The methanol was removed *in vacuo*, and the residue was carefully acidifed with 2N aq. HCl. The resulting precipitate was collected by filtration, and triturated with ethyl acetate to give 2-amino-5-cyanobenzoic acid as a pale brown solid (4.8g, 29.6mmol, 34%); δH [$^2H_6$]DMSO 8.02 (1H,d), 7.55 (1H,dd), 7.50 (2H,br s), 6.86 (1H,d).

6-Cyano-quinazolinone

A stirred solution of 2-amino-5-cyanobenzoic acid (2.0g, 12.3mmol) in formamide (10ml) was heated at 190°C for 7 hours. The dark solution was allowed to cool and poured into water (50ml). The resulting precipitate was collected by filtration and dried *in vacuo* at 60°C to give 6-cyanoquinazolinone (0.93g, 5.43mmol, 44%); [$^2H_6$]DMSO 12.65 (1H,s), 8.50 (1H,s), 8.28 (1H,s), 8.18 (1H,dd), 7.81(1H,d).

(4-Benzyloxy-phenyl)-(6-(trimethylsilylethynyl)quinazolin-4-yl)-amine

The (4-benzyloxy-phenyl)-(6-iodoquinazolin-4-yl)-amine hydrochloride (1.0g, 2.04mmol) was reacted with trimethylsilylacetylene (8.0ml, 5.56g, 5.66mmol), triethylamine (5.0ml, 3.63g, 3.58mmol), bis(triphenylphosphine)palladium (II) chloride (0.10g, 0.14mmol) and copper(I)iodide (0.10g, 0.53mmol) at room temperature in acetonitrile (15ml) under a nitrogen atmosphere overnight. Purification by silica gel chromatography (eluting with 50% *i*-hexane/EtOAc) gave the title compound as an off-white solid (0.70g, 1.65mmol, 81%).

(4-Benzyloxy-phenyl)-(6-ethynylquinazolin-4-yl)-amine

The (4-benzyloxy-phenyl)-(6-(trimethylsilylethynyl)quinazolin-4-yl)-amine (0.65g, 1.53mmol) was reacted with tetrabutylammonium fluoride in tetrahydrofuran (1.0M, 5.0ml, 5.0mmol) at room temperature for 20 min. The solvent was removed *in vacuo*, and the residual oil was partitioned between water (20ml) and ethyl acetate (20ml). After separation, the aqueous was extracted with further ethyl acetate (2x20ml). The combined organic solutions were dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as an off-white solid (0.43g, 1.22mmol, 80%).

N-Methyl-*N*-(2-methylsulphonylethyl)amine hydrochloride

Methylvinyl sulphone (2.1g, 19.78mmol) and methylamine (33% solution in IMS, 40ml, excess) were mixed and heated at reflux under a nitrogen atmosphere for 6 hours. After standing overnight at room temperature, the mixture was concentrated *in vacuo* to give a yellow oil, which was treated with ethereal HCl to give a sticky solid. Trituration with absolute ethanol gave the title compound as a white solid which was collected by filtration and dried at 60°C *in vacuo* (1.01g, 5.82mmol, 29%); δH [$^2H_6$]DMSO 9.27 (2H,br s), 3.59 (2H,dd), 3.31 (2H,dd), 3.12 (3H,s), 2.57 (3H,s).

N-[2-(Methylsulphonamido)ethyl]acetamide

N-Acetyethylenediamine (10.2g, 100mmol) and triethylamine (15ml, 10.9g, 108mmol) were dissolved in dichloromethane (300ml) and the solution cooled to 0°C. Methane sulphonyl chloride (8ml, 11.8g, 103mmol) was dissolved in dichloromethane (10ml) and added dropwise , and stirring was continued at 0°C for 3 hours. The dichloromethane was removed *in vacuo*, and the residue was suspended in a mixture of ether and acetone, removing the insoluble material by filtration. The filtrate was concentrated *in vacuo* to give the title compound as a pale brown gum (14.5g, 88.3mmol, 88%); δH [$^2H_6$]DMSO 7.93 (1H,br t), 7.05 (1H,t), 3.11 (2H,t), 2.97 (2H,t), 2.89 (3H,s), 2.09 (3H,s).

2-(Methylsulphonamido)ethylamine hydrochloride

N-[2-(Methylsulphonamido)ethyl]acetamide (14.5g, 88.3mmol) and concentrated hydrochloric acid (100ml) were dissolved in water (100ml) and heated to reflux for a total of 3 hours. After cooling, the water was removed *in vacuo*, and the residue was left for several days at room temperature until crystallisation was underway. Trituration with a mixture of ethanol and ether gave the title compound as a white solid which was dried *in vacuo* at 60°C (7.5g, 42.9mmol, 49%); δH [$^2H_6$]DMSO 8.22 (2H,br s), 7.42 (1H,t), 3.23 (2H,q), 2.87 (3H,s), 2.85-2.95 (2H,m).

2-Phthalamidoethylsulphonamide

2-Phthalamidoethylsulphonyl chloride (prepared as described in J. Am. Chem. Soc., 69, 1393-1401, (1947)) (10.0g, 36.5mmol) was added to conc. aqueous ammonia solution (0.880Mol, 120ml), cooled to 0°C. The mixture was stirred at 0°C for 30 min and then at room temperature for 2 hours. Concentration *in vacuo*, followed by trituration with water gave 2-phthalamidoethylsulphonamide as a white solid (3.70g,

14.6mmol, 40%); δH [$^2H_6$]DMSO 7.80-7.92 (4H,m), 7.03 (2H,br s), 3.96 (2H,dd), 3.30-3.38 (2H,m, obscured by water).

2-Aminoethylsulphonamide hydrochloride

2-Phthalamidoethylsulphonamide (3.68g, 14.5mmol) was suspended in ethanol (50ml) and hydrazine hydrate (0.70g, 71.5mmol) was added. The mixture was heated to reflux for 4 hours. The mixture was partially concentrated *in vacuo*, diluted with water, acidified to pH 1 with 2N HCl, and filtered. The filtrate was concentrated *in vacuo* to give a white solid. Treatment with more 2N HCl, followed by trituration with a mixture of ethanol and acetone gave the title compound as a white solid (1.0g, 6.23mmol, 43%); δH D_2O 3.60-3.69 (2H,m), 3.50-3.58 (2H,m).

(3-Methyl-3-oxetane)methyl 2-furoate

2-Furoic acid (9.0g, 80.3mmol) was added to a solution of 3-methyl-3-oxetanemethanol (16.5g, 161.6mmol), 1,3-dicyclohexylcarbodiimide (25.0g, 121.1mmol) and DMAP (0.50g, 4.1mmol) in dichloromethane (250ml), and the mixture was stirred under a nitrogen atmosphere overnight. The mixture was filtered and the filtrate was concentrated *in vacuo* to give an oil. Crystallisation from ethanol/water gave a white solid collected by filtration and shown by NMR to be 2-furoic acid. The filtrate was concentrated *in vacuo* to remove the ethanol, and the resulting aqueous solution was extracted with dichloromethane (x2). This solution was dried ($MgSO_4$) and concentrated to give the title compound as a colourless oil (11.8g, 60.1mmol, 75%); δH [$^2H_6$]DMSO 8.00 (1H,s), 7.34 (1H,d), 7.71 (1H, dd), 4.44 (2H,d), 4.35 (2H,s), 4.28 (2H,d), 1.31 (3H,s).

2-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)furan

(3-Methyl-3-oxetane)-methyl-2-furoate (11.8g, 60.1mmol) was dissolved in dichloromethane (250ml) and the solution was cooled to 0°C. Boron trifluoride-etherate (10 drops) was added and the mixture stirred at room temperature, and then left to stand for two months. Triethylamine (0.5ml, 0.36g, 3.6mmol) was added and the mixture concentrated to give a sticky white solid. Trituration with ether/acetone gave the title compound as a white solid (2.2g, 11.2mmol, 19%); δH [$^2H_6$]DMSO 8.00 (1H,s), 7.34 (1H,d), 7.71 (1H, dd), 4.44 (2H,d), 4.35 (2H,s), 4.28 (2H,d), 1.31 (3H,s).

5-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-2-[tri(*n*-butyl)stannyl]furan

2-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)furan (2.0g, 10.2mmol) was dissolved in THF (20ml) and the solution was cooled to -78°C. *n*-BuLi (1.6M solution in hexanes, 7.7ml, 12.32mmol) was added and the mixture stirred at -78°C for 30min, allowed to warm to 0°C for 20 min. and then recooled to -78°C. The tributyltin chloride (3.5ml, 4.68g, 14.4mmol) was added and stirring was continued at -78°C for 15min. The mixture was allowed to warm gradually to room temperature and stirring continued for three days. The reaction was quenched by the addition of water, and extracted with ethyl acetate. This solution was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound as a yellow oil (4.7g, 9.7mmol, 95%); δH [$^2H_6$]DMSO 6.52 (1H,d), 6.38 (1H, d), 3.96 (6H,s), 0.77-1.63 (30H,m).

(4-Benzyloxy-phenyl)-(6-[5-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)furan-2-yl]quinazolinyl)-amine

(4-Benzyloxy-phenyl)-(6-iodoquinazolin-4-yl)-amine (0.925g, 2.04mmol), 5-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-2-[tri(*n*-butyl)stannyl]furan (2.00g, 4.1mmol) and bis(triphenylphosphine)palladium (II) chloride (catalytic) were reacted in dry dioxane (25ml) according to Procedure B. Purification by silica gel chromatography and eluting with 100% EtOAc gave the title compound as a yellow solid (0.700g, 1.34mmol, 66%); δH [$^2H_6$]DMSO 10.0 (1H,s), 8.75 (1H,s), 8.48 (1H,s), 8.12 (1H,d), 7.79 (1H,d), 7.66 (2H,d), 7.30-7.52 (5H,m), 7.03-7.12 (3H,m), 6.64 (1H,d), 5.14 (2H,s), 4.06 (6H,s), 0.85 (3H,s).

(4-(4-Benzyloxyanilino)quinazolin-6-yl)-(*N*-hydroxycarboximidamide)

Sodium hydroxide (0.62g, 15.5mmol) and hydroxylamine hydrochloride (1.03g, 14.8mmol) were added to a solution of (4-benzyloxy-phenyl)-(6-cyanoquinazolin-4-yl)-amine (0.472g, 1.34mmol) in ethanol (30ml), and the resulting mixture was heated to reflux overnight. After cooling, the mixture was concentrated *in vacuo*. The residue was washed thoroughly with water, and then with a little ether and dried *in vacuo* to give the title amidoxime (0.452g,1.18mmol, 88%); δH [$^2H_6$]DMSO 9.88 (1H,s), 9.73 (1H,s), 8.72 (1H,s), 8.52 (1H,s), 8.13 (1H,d), 7.67-7.78 (3H,m), 7.31-7.52 (5H,m), 7.07 (2H,d), 6.65 (2H,s), 5.14 (2H,s);m/z ($M+1^+$) 386.

(4-(1-Benzyl-1H-indazol-5-yl)quinazolin-6-yl)-(*N*-hydroxycarboximidamide)

Sodium hydroxide (0.563g, 14.1mmol) and hydroxylamine hydrochloride (0.931g, 13.4mmol) were added to a solution of (1-benzyl-1H-indazol-5-yl)-(6-cyanoquinazolin-4-yl)-amine (0.504g, 1.34mmol) in ethanol (40ml), and the resulting mixture was heated to reflux overnight. After cooling, the mixture was concentrated *in vacuo* . The residue was washed thoroughly with water, and then with a little ether and dried *in vacuo* to give the title amidoxime (0.452g,1.10mmol, 82%); δH [$^2H_6$]DMSO 9.87 (2H,m), 8.76 (1H,s), 8.54 (1H,s), 8.23 (1H,s), 8.10-8.18 (2H,m), 7.65-7.80 (3H,m), 7.18-7.38 (5H,m), 5.96 (2H,s), 5.68 (2H,s); m/z ($M+1^+$) 410.

N-(2-Methylthioethyl)-trifluoroacetamide

Trifluoroacetic anhydride (17ml, 25.28g, 120.6mmol) was added dropwise to a solution of 2-methylthioethylamine (10.0g, 109.7mmol) and triethylamine (16.8ml, 12.2g, 120.5mmol) in anhydrous dichloromethane (50ml) cooled to 0°C using an ice bath. On completion of the addition, the reaction was stirred at room temperature under a nitrogen atmosphere for 18 hours. Water (200ml) was added, the layers were separated, and the aqueous was extracted with further dichloromethane (100ml). The combined dichloromethane solutions were dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound as a yellow oil (19.0g, 109.7mmol, 100%); δH $CDCl_3$ 6.8 (1H,br s), 3.59 (2H,q), 2.72 (2H,t), 2.13 (3H,s).

N-(2-Methylsulphonylethyl)-trifluoroacetamide

A solution of *N*-(2-methylthioethyl) trifluoroacetamide (19.0g, 109.7mmol) in methanol (200ml) was cooled to 0°C using an ice bath. A suspension of Oxone™ ($2KHSO_5.KHSO_4.K_2SO_4$) (74.19g, 120.67mmol) in water (100ml) was added portionwise over 10 minutes, and the reaction was stirred at room temperature for 24 hours. The methanol was removed *in vacuo*, water (600ml) was added and the mixture was extracted with dichloromethane (3 x 300ml). The combined extracts were dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound as a white solid (12.42g, 56.7mmol, 52%); δH $CDCl_3$ 7.33 (1H,br s), 3.93 (2H,q), 3.31 (2H,t), 3.02 (3H,s).

N-(Ethoxycarbonylmethyl)-*N*-(2-methylsulphonylethyl)-trifluoroacetamide

Sodium hydride (60% dispersion in mineral oil, 0.190g, 4.75mmol) was added to a solution of *N*-(2-methylsulphonylethyl) trifluoroacetamide (0.986g, 4.50mmol) in dry

DMF (10ml) and the mixture was stirred under a nitrogen atmosphere for 30 minutes. Ethyl bromoacetate (0.55ml, 0.828g, 4.96mmol) was added and the mixture was stirred at room temperature overnight. The mixture was poured into ice-water, and extracted with ethyl acetate. This solution was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound as a white solid (1.239g, 4.03mmol, 90%); δH $CDCl_3$ 4.17 (4H,m), 3.91 (2H,t), 3.46 (2H,t), 2.98 (3H,s), 1.30 (3H,t).

Methyl 2-(4-piperidon-1-yl)acetate

A solution of methyl bromoacetate (13.6ml, 21.98g, 144mmol) in acetonitrile (20ml) was added to a mixture of 4-piperidone monohydrate hydrochloride (20g, 130mmol) and potassium carbonate (36g, 260mmol) in more acetonitrile (100ml). The mixture was heated at reflux under a nitrogen atmosphere for 18 hours. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and water, and the aqueous extratced with further EtOAc. The organic solution was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give methyl 2-(4-piperidon-1-yl)acetate as a yellow oil (14.29g, 83.5mmol, 64%); tlc (SiO_2, 1:1 EtOAc/hexane, Rf = 0.23).

1-(N,N-Dimethylaminopropyl)-imidazole

Imidazole (10.9g) was treated with sodium hydroxide (10.9g) in acetonitrile (80ml) at room temperature for 30 minutes. Tetra-N-butyl ammonium hydrogen sulphate (2.16g) was added and 3-N,N-dimethylaminopropyl chloride hydrochloride (27.19g). After 24 hours at reflux, the cooled mixture was concentrated, filtered and concentrated *in vacuo*. Chromatography on silica gave the title compound (19.82g) as a red oil; δH $CDCl_3$ 7.48 (1H,s), 7.04 (1H,s), 6.91 (1H,s), 4.01 (2H,t), 2.11(6H,s), 2.10 (2H,t), 1.91 (2H,m).

1-(N,N-Dimethylaminopropyl)-5-tri-n-butylstannylimidazole

1-(N,N-Dimethylaminopropyl)-imidazole (3g) was added to a mixture of TMEDA (7ml) and n-butyl lithium (29.4ml, 1.6M) in n-hexane (25ml) at -20°C under nitrogen.After 30 minutes at -20°C and 30 minutes at 20°C, the mixture was recooled to -20°C and tri-n-butylstannyl chloride (13.05ml) was added dropwise. The mixture was allowed to warm to 20°C and stirred there for 20 hours. The mixture was partitioned between ethyl acetate and water, the aqueous phase was

extracted with ethyl acetate and combined organic extracts were dried and concentrated. Purification by flash chromatography gave the title compound (2.10g); δH $CDCl_3$ 7.70 (1H,s), 7.01 (1H,s), 3.98 (2H,t), 2.20(6H,s), 2.20 (2H,t), 1.90 (2H,m) 1.55 (6H,m), 1.37 (12H,m), 0.92 (9H,m).

1-(N,N-Dimethylaminopropyl)-2-tri-n-butylstannylimidazole

1-(N,N-Dimethylaminopropyl) imidazole (2g) in THF (20ml) at -78°C was treated with nBuLi (8.6ml, 1.6M) under nitrogen. After 30 minutes at -78°C, tri-n-butylstannyl chloride was added and the mixture allowed to warm to 20°C. The mixture was concentrated *in vacuo*, taken up in n-hexane and filtered. The filtrate was concentrated *in vacuo* to give the title compound (4.33g) as a yellow oil; δH $CDCl_3$ 7.28 (1H,s), 7.09 (1H,s), 3.97 (2H,t), 2.25 (2H,t), 2.20(6H,s), 1.90 (2H,m) 1.55 (6H,m), 1.34 (12H,m), 0.92 (9H,m).

(4-Hydroxy-quinazolin-7-yl)-carboxylic acid

3-Amino-1,4-dibenzoic acid (8.6g) was heated at 180°C in formamide (30ml) for 2 hours. The mixture was allowed to cool and filtered, washing with acetone to give the title compound (9.1g); R.T. (LC), 3.33mins.

4-Hydroxy quinazoline-7-hydrazide

(4-Hydroxy-quinazolin-7-yl)-carboxylic acid (0.5g) In dry THF (20ml) was treated with carbonyl diimidazole (0.85g) under nitrogen for 6 hours at room temperature. Hydrazine hydrate was added and stirring was continued for 18 hours. The mixture was filtered to give the title compound (0.41g); m/z (M+1+) 205.

7-(5-Methyl-[1,3,4]oxadiazol-2-yl)quinazolin-4-one

4-Hydroxy quinazoline-7-hydrazide (0.41g) was treated with triethyl orthoacetate (10ml) at reflux under nitrogen for 24 hours. The mixture was cooled, filtered and purified by chromatography to give the title compound (0.09g); m/z (M+1+) 229.

4-Chloro-7-(5-methyl-[1,3,4]oxadiazol-2-yl)quinazoline

7-(5-Methyl-[1,3,4]oxadiazol-2-yl)quinazolin-4-one (0.09g) was treated with phosphorous oxychloride (5ml) at reflux under nitrogen for 2 hours. The mixture was cooled, evaporated and partitioned between saturated aqueous sodium carbonate

and ethyl acetate. The organic phase was dried, concentrated in vacuo to give the title compound which was used crude in the subsequent synthetic step.

7-Iodoquinazolin-4-one

7-Amino-quinazolin-4-one (R. Dempcy and E. Skito, Biochemistry, 30, 1991, 8480) (1.61g) was suspended in 6N HCl (20ml) and cooled in an ice bath. A solution of sodium nitrite (0.75g) in water (10ml) was added dropwise over 15 minutes. After a further 10 minutes, a solution of potassium iodide (1.66g) in water (5ml) was added dropwise. The mixture was warmed to 20°C and after 3 hours partitioned between ethyl acetate and sodium thiosulphate. The organic phase was dried and concentrated in vacuo to give the title compound (0.485g); m/z (M+1+) 271.

4-Chloro-7-iodoquinazoline

7-Iodoquinazolin-4-one (0.46g) was treated with phosphorous oxychloride (5ml) at reflux under nitrogen for 2 hours. The mixture was cooled, evaporated and partitioned between saturated aqueous sodium carbonate and ethyl acetate. The organic phase was dried and concentrated in vacuo to give the title compound (0.43g); m/z (M+1+) 291.

(1-Benzyl-1H-indazol-5-yl)-(7-iodoquinazolin-4-yl)-amine hydrochloride

4-Chloro-7-iodoquinazoline (0.42g) was treated with 1-benzyl-1H-indazol-5-ylamine (0.323g) in acetonitrile (20ml) at reflux under nitrogen for 18 hours (Procedure A). The mixture was cooled and filtered to give the title compound (0.57g); m/z (M+1+) 478.

Examples

Example 1

(4-Benzyloxy-phenyl)-(6-furan-2-yl-quinazolin-4-yl)-amine (Procedure B)

The (4-benzyloxy-phenyl)-(6-bromo-quinazolin-4-yl)-amine (300mg, 0.74mmol), 2-(tributylstannyl)furan (290mg, 0.81mmol) and bis(triphenylphosphine) palladium(II) chloride (catalytic) were dissolved in dioxane (3.5ml) and heated at reflux under nitrogen for 2 hr. The cooled reaction mixture was absorbed onto silica and purified by flash column chromatography (silica gel, eluting with 1:1 ethyl acetate/iso-hexane) to give the title product (290mg, 79%) as a pale yellow solid; δH [$^2H_6$]-DMSO 9.94 (1H, b, NH), 8.85 (1H, s, 5-H), 8.53 (1H, s, 2-H), 8.21

(1H, d, 7-H), 7.91 (1H, d, furan-H), 7.81 (1H, d, 8-H), 7.72 (2H, d, 2'-H, 6'-H), 7.57-7.33 (5H, m, 5 x Ph-H), 7.16 (1H, d, furan-H), 7.10 (2H, d, 3'-H, 5'-H), 6.72, (1H, dd, furan-4H), 5.17 (2H, s, CH_2); m/z 394 $(M+1)^+$.

Example 2

(4-Benzyloxy-phenyl)-(6-(thiophen-2-yl)-quinazolin-4-yl)-amine (Procedure B)

The (4-benzyloxy-phenyl)-(6-bromoquinazolin-4-yl)-amine (200mg, 0.49mmol), 2-(tributylstannyl)thiophene (200mg, 0.53mmol) and bis(triphenylphosphine) palladium(II) chloride (catalytic) were dissolved in dioxan (3ml) and heated at reflux under nitrogen for 4 hr. The cooled reaction mixture was absorbed onto silica and purified by flash column chromatography (silica gel, eluting with an ethyl acetate/iso-hexane gradient). The resulting solid was triturated with iso-hexane/ethyl acetate to give the product (120mg, 60%) as a pale yellow solid; δH $[^2H_6]$-DMSO 9.88 (1H, b, NH), 8.76 (1H, s, 5-H), 8.49 (1H, s, 2-H), 8.12 (1H, d, 7-H), 7.82-7.60 (5H, m, thiophene-3-H, thiophene-5-H, 8-H, 2'-H, 6'-H), 7.52-7.30 (5H, m, 5 x Ph-H), 7.23 (1H, t, thiophene-4H), 7.18 (2H, d, 3'-H, 5'-H), 5.11 (2H, s, CH_2); m/z 410 $(M+1)^+$.

Example 3

(4-Benzyloxy-phenyl)-(6-(pyridin-2-yl)-quinazolin-4-yl)-amine (Procedure B)

The (4-benzyloxy-phenyl)-(6-bromoquinazolin-4-yl)-amine (200mg, 0.49mmol), 2-(tributylstannyl)pyridine (200mg, 0.53mmol) and bis(triphenylphosphine) palladium(II) chloride (catalytic) were dissolved in dioxan (3ml) and heated at reflux under nitrogen for 9 hr. The cooled reaction mixture was absorbed onto silica and purified by flash column chromatography (silica gel, eluting with an ethyl acetate/iso-hexane gradient). The resulting solid was triturated with iso-hexane/ethyl acetate to give the product (110mg, 56%) as a pale yellow solid; δH $[^2H_6]$-DMSO 9.99 (1H, b, NH), 9.18 (1H, s, 5-H), 8.76 (1H, d, pyridine-H), 8.60 (1H, d, 7-H), 8.54 (1H, s, 2-H), 8.23 (1H, d, pyridine-H), 8.00 (1H, t, pyridine-H), 7.87 (1H, d, 8-H), 7.70 (2H, d, 2'-H, 6'-H), 7.53-7.31 (6H, m, 5 x Ph-H, pyridine-H), 7.09 (2H, d, 3'-H, 5'-H), 5.14 (2H, s, CH_2); m/z 405 $(M+1)^+$.

Example 4

(4-Benzyloxy-phenyl)-(6-(pyrimidin-2-yl)-quinazolin-4-yl)-amine

The (4-benzyloxy-phenyl)-(6-bromoquinazolin-4-yl)-amine (200mg, 0.49mmol), 2-(tributylstannyl)pyrimidine (200mg,0.54mmol) and bis(triphenylphosphine)

palladium(II) chloride (catalytic) were dissolved in dioxan (3ml) and heated at reflux under nitrogen for 27 hr (Procedure B). The solvent was removed from the cooled reaction under vacuum, and the residue was purified by flash column chromatography (silica gel, eluting with an ethyl acetate/iso-hexane gradient). The resulting oily solid was triturated with iso-hexane/ethyl acetate to give the product (80mg, 40%) as a pale yellow solid; δH [$^2H_6$]-DMSO 10.30 (1H, b, NH), 9.61 (1H, s, 5-H), 9.07 (2H, d, pyrimidine 4-H, pyrimidine 6-H), 8.86 (1H, d, 7-H), 8.51 (1H, s, 2-H), 7.93 (1H, d, 8-H), 7.78 (2H, d, 2'-H, 6'-H), 7.65-7.36 (6H, m, 5 x Ph-H, pyrimidine 5-H), 7.11 (2H, d, 3'-H, 5'-H), 5.18 (2H, s, CH_2); m/z 406 $(M+1)^+$.

Example 5

(4-Benzyloxy-phenyl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl-quinazolin-4-yl)-amine

(Procedure B)

The (4-benzyloxy-phenyl)-(6-bromoquinazolin-4-yl)-amine (1.5g, 3.7mmol), 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)-furan (1.9g, 4.42mmol) and bis(triphenylphosphine)palladium(II) chloride (catalytic) were dissolved in dioxan (30ml) and heated at reflux under nitrogen for 6 hr. The solvent was removed from the cooled reaction under vacuum, and the residual oil was triturated with iso-hexane/ethyl acetate to give the product (1.07g, 62%) as a pale yellow solid; δH [$^2H_6$]-DMSO 9.96 (1H, b, NH), 8.80 (1H, s, 5-H), 8.51 (1H, s, 2-H), 8.18 (1H, d, 7-H), 7.80 (1H, d, 8-H), 7.70 (2H, d, 2'-H, 6'-H), 7.58-7.30 (5H, m, 5 x Ph-H), 7.10 (3H, m, 3'-H, 5'-H, furan 3-H), 6.78 (1H, d, furan 4-H), 6.12 (1H, s, $CH0_2$), 5.18 (2H, s, $PhCH_2$), 4.22-3.94 (4H, m, 2 x CH_2); m/z 466 $(M+1)^+$.

Example 6

(4-Benzyloxy-phenyl)-(6-(3-methyl-3H-imidazol-4-yl)-quinazolin-4-yl)-amine

The (4-benzyloxy-phenyl)-(6-bromoquinazolin-4-yl)-amine (1.0g, 2.46mmol), 1-methyl-5-(tributylstannyl)imidazole (prepared according to Gaare, K., *et al.* Acta Chem. Scand. (1993), 47(1), 57-62) (1.25g, 3.37mmol) and bis(triphenylphosphine)palladium (II) chloride (catalytic amount) were reacted according to Procedure B in dioxane (50ml) for 3 hours. The solvent was removed *in vacuo*, and the solid was washed with *i*-hexane. The resulting dark solid was suspended in IMS, and undissolved material removed by filtration. The resulting filtrate was concentrated *in vacuo* to give the product as a pale baige

solid (0.90g, 2.21mmol, 90%); δH [$^2H_6$]-DMSO 9.69 (1H, b, NH), 8.60 (1H, s, 5-H), 8.55 (1H, s, 2-H), 8.00 (1H, d, 7-H), 7.83 (2H, m, 8-H, imidazole-H), 7.69 (2H, d, 2'-H, 6'-H), 7.52-7.33 (5H, m, 5 x Ph-H), 7.22 (1H, s, imidazole-H), 7.09 (2H, d, 3'-H, 5'-H), 5.14 (2H, s, CH_2), 3.80 (3H, s, CH_3); m/z 408 $(M+1)^+$.

Example 7

(4-Benzyloxy-phenyl)-(6-(2,3-dihydrofuran-5-yl)-quinazolin-4-yl)-amine

The (4-benzyloxy-phenyl)-(6-bromoquinazolin-4-yl)-amine (200mg, 0.49mmol), 5-(tributylstannyl)-2,3-dihydrofuran (250mg, 0.70mmol) and bis(triphenylphosphine)palladium(II) chloride (catalytic) were dissolved in dioxan (10ml) and heated at reflux under nitrogen for 2 hr (Procedure B). The solvent was removed from the cooled reaction under vacuum, and the residue was suspended in 1:1 iso-hexane/ethyl acetate and filtered. The solvent was removed from the filtrate under vacuum to give the product (140mg, 72%) as a yellow solid; δH [$^2H_6$]-DMSO 9.88 (1H, b, NH), 8.62 (1H, s, 5-H), 8.50 (1H, s, 2-H), 8.05 (1H, d, 7-H), 7.67 (3H, m, 8-H, 2'-H, 6'-H), 7.55-7.29 (5H, m, 5 x Ph-H), 7.03 (2H, m, 3'-H, 5'-H), 5.81 (1H, s, 3"-H), 5.12 (2H, s, $PhCH_2$), 4.52 (2H, t, 5"-H_2), 2.88 (2H, t, 4"-H_2); m/z 396 $(M+1)^+$.

Example 8

(4-Benzyloxy-phenyl)-(6-(3-methyl-1,2,3-triazol-4-yl)-quinazolin-4-yl)-amine

(Procedure B)

The (4-benzyloxy-phenyl)-(6-bromoquinazolin-4-yl)-amine (250mg, 0.62mmol), 1-methyl-5-(tributylstannyl)-1,2,3-triazole (300mg, 0.81mmol) and bis(triphenylphosphine)palladium(II) chloride (catalytic) were dissolved in dioxan (10ml) and heated at reflux under nitrogen for 48 hr. The solvent was removed from the cooled reaction under vacuum, and the residue was triturated with iso-hexane. The resulting material was dissolved in ethyl acetate, filtered and the filtrate evaporated to dryness. Trituration with ethyl acetate/iso-hexane gave the product (115mg, 45%) as a beige solid; δH [$^2H_6$]-DMSO 9.90 (1H, b, NH), 8.76 (1H, s, 5-H), 8.61 (1H, s, 2-H), 8.10 (2H, m, 7-H, triazole-H), 7.92 (1H, d, 8-H), 7.70 (2H, d, 2'-H, 6'-H), 7.58-7.38 (5H, m, 5 x Ph-H), 7.12 (2H, d, 3'-H, 5'-H), 5.19 (2H, s, CH_2), 4.22 (3H, s, CH_3); m/z 409 $(M+1)^+$.

Example 9

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde

The 4-(4-benzyloxy-phenylamino)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-quinazolin-4-yl)-amine (1.0g, 2.1mmol) was dissolved in THF (20ml) and hydrochloric acid (2N, 10ml) was added. The reaction was stirred at room temperature for 1 hr. The precipitate which formed was collected by filtration and washed with acetone, then partitioned between ethyl acetate, triethylamine and water. The organic phase was washed with water, dried (magnesium sulphate) and the solvent was removed under vacuum. Trituration with iso-hexane/ethyl acetate gave the product as an orange solid (610mg, 69%); δH [$^2H_6$]-DMSO 10.05 (1H, b, NH), 9.62 (1H, s, CHO), 8.95 (1H, s, 5-H), 8.48 (1H, s, 2-H), 8.24 (1H, d, 7-H), 7.80 (1H, d, 8-H), 7.70 (1H, d, furan 4-H), 7.59 (2H, d, 2'-H, 6'-H), 7.48-7.25 (6H, m, 5 x Ph-H, furan 3-H), 7.02 (2H, m, 3'-H, 5'-H), 5.09 (2H, s, CH_2); m/z 422 $(M+1)^+$.

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride

4-(4-Benzyloxy-phenylamino)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-quinazolin-4-yl)-amine (6.70g, 14.4mmol) was stirred at room temperature in a mixture of THF (70ml) and 2N aqueous HCl (70ml) for 1 hour. The THF was removed *in vacuo* and the resulting precipitate was collected by filtration and washed with water to give the hydrochloride salt as a yellow solid (6.50g, 14.1mmol, 98%); δH [$^2H_6$]DMSO 12.15 (1H,s), 9.69 (1H,s) 9.58 (1H,s), 8.88 (1H,s), 8.50 (1H,dd), 8.02 (1H,d), 7.77 (1H,d), 7.62-7.74 (3H,m), 7.31-7.52 (5H,m), 7.15 (2H,d), 5.17 (2H,s).

Example 10

(4-Benzyloxy-phenyl)-(6-(5-(4-methylpiperazin-1-ylmethyl)-furan-2-yl)- quinazolin-4-yl)-amine

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde (0.19g) and 1-methylpiperazine (0.056g) were mixed in dichloromethane (0.6ml) and stirred at room temperature for 5 mins. The mixture was chilled to 0°C and sodium triacetoxyborohydride (0.5g) added in portions with stirring. The reaction was stirred at 0°C for 2 hr. The reaction was quenched with water and extracted with dichloromethane (x2). The combined organic fractions were dried (magnesium sulphate) and the solvent removed under vacuum. The resulting orange glass was triturated with ethyl acetate / iso-hexane. The solid produced was filtered off and

dried at 60°C under vacuum to give the product as a yellow solid (0.11g); δH [$^2H_6$] -DMSO 10.89 (1H, b), 8.70 (1H, s), 8.47 (1H, s), 8.11 (1H, d), 7.77 (1H, d), 7.66 (2H, d), 7.50-7.30 (5H, m), 7.12-7.00 (3H, m), 6.50 (1H, d), 5.13 (2H, s), 3.58 (2H, s), 2.53-2.22 (8H, m), 2.12 (3H, s); m/z 506 $(M+1)^+$.

Example 11

(S)-1-(5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-pyrrolidine-2-carboxylic acid amide

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde and L-prolinamide were reacted in an analogous manner to Example 10 to give the title compound; δH [$^2H_6$] -DMSO 9.85 (1H, b), 8.72 (1H, s), 8.50 (1H, s), 8.14 (1H, d), 7.79 (1H, d), 7.71 (2H, d), 7.54-7.31 (5H, m), 7.24 (1H, s), 7.17 (1H, s), 7.09 (2H, d), 7.02 (1H, d), 6.53 (1H, d), 5.15 (2H, s), 3.82 (2H, s), 3.42 (1H, b), 3.12 (2H, b), 1.85-1.67 (4H, m); m/z 520 $(M+1)^+$.

Acidification with ethereal HCl gave a yellow precipitate, which was dissolved in MeOH. This solution was concentrated *in vacuo* and the residue was triturated with ether to give the product as a yellow solid which was dried at 60°C *in vacuo* to give the hydrochloride salt as a yellow solid; δH [$^2H_6$]DMSO 12.35 (1H,s), 9.64 (1H,s), 8.86 (1H,s), 8.42 (1H,d), 8.30 (1H,s), 8.00 (1H,d), 7.68-7.76 (3H,m), 7.31-7.55 (6H,m), 7.14 (2H,d), 6.89 (1H,d), 5.18 (2H,s), 4.57 (2H,s), 3.50-3.70 (3H,m), 1.80-2.10 (4H,m); m/z $(M+1^+)$ 520.

Example 12

N2-(5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-N1,N1-dimethyl-propane-1,2-diamine

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde and *N,N*-dimethyl-1,2-propanediamine were reacted in an analogous manner to Example 10 to give the title compound; δH [$^2H_6$] -DMSO 9.83 (1H, b,), 8.70 (1H, s), 8.42 (1H, s), 8.10 (1H, d), 7.73 (1H, d), 7.64 (2H, d), 7.50-7.28 (5H, m), 7.02 (2H, d), 6.99 (1H, d), 6.52 (1H, d), 5.10 (2H, s), 3.93-3.70 (2H, m), 2.04 (9H, m), 0.92 (3H, m); m/z 508 $(M+1)^+$.

Example 13

N-(5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-N-ethyl-N',N'-dimethyl-ethane-1,2-diamine

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde and *N*-ethyl-*N'*,*N'*-dimethyl-ethane-1,2-diamine were reacted in an analogous manner to Example 10 to give the title compound; δH [$^2H_6$] -DMSO 9.90 (1H, b), 8.79 (1H, s), 8.48 (1H, s), 8.12 (1H, d), 7.79 (1H, d), 7.70 (2H, d), 7.53-7.31 (5H, m), 7.12-7.02 (3H, m), 6.04 (1H, d), 5.13 (2H, s), 3.80 (2H, s), 2.68 (4H, s), 2.55 (2H, q), 2.36 (6H, s), 1.09 (3H, t); m/z 522 $(M+1)^+$.

Example 14

(4-Benzyloxy-phenyl)-(6-(5-(pyridin-3-ylaminomethyl)-furan-2-yl)quinazolin-4-yl)-amine

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde and 3-aminopyridine were reacted in an analogous manner to Example 10 to give the title compound; δH [$^2H_6$] -DMSO 9.82 (1H, b), 8.70 (1H, s), 8.42 (1H, s), 8.11-8.01 (2H, m), 7.80-7.70 (2H, m), 7.62 (2H, d), 7.49-7.25 (5H, m), 7.10-6.95 (5H, m), 6.48 (1H, d), 6.40 (1H, t), 5.10 (2H, s), 4.38 (2H, d); m/z 500 $(M+1)^+$.

Example 15

(4-Benzyloxy-phenyl)-(6-(5-(((tetrahydro-furan-2-ylmethyl)-amino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine hydrochloride

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde and tetrahydro-furfuralamine were reacted in an analogous manner to Example 10 to give the title compound; δH [$^2H_6$] -DMSO (of the free base) 9.82 (1H, s), 8.69 (1H, s), 8.41 (1H, s), 8.10 (1H, d), 7.71(1H, d), 7.62 (2H, d), 7.50-7.25 (5H, m), 7.10-7.06 (3H, m), 6.42 (1H, d), 5.10 (2H, s), 3.91-3.50 (9H, m), 2.60 (2H, d); m/z 507 $(M+1)^+$.

Example 16

(1-Benzyl-1H-indazol-5-yl)-(6-(5-(1,3)-dioxolan-2-yl-furan-2-yl)-quinazolin-4-yl)-amine

(1-Benzyl-1H-indazol-5-yl)-(6-bromoquinazolin-4-yl)-amine (4.3g), 2-(tributylstannyl)-5-(1,3-dioxolan-2-yl)-furan (J. Chem. Soc., Chem Commun., (1988), 560) (10g) and 1,4-bis(diphenylphosphino) palladium (II) chloride (1g) were heated at reflux in dioxane (150ml) for 24 hr. The solvent was removed *in vacuo* and the residue chromatographed on silica. Subsequent trituration gave the title compound δH [$^2H_6$]

-DMSO 10.13 (1H, s), 8.85 (1H, s), 8.54 (1H, s), 8.20 (3H, m), 7.80 (3H, m), 7.30 (5H, m), 7.13 (1H, d), 6.79 (1H, d), 6.04 (1H, s), 5.71 (2H, s), 4.15 (4H, m).

Example 17

5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride

(1-Benzyl-1H-indazol-5-yl)-(6-(5-(1,3)-dioxolan-2-yl-furan-2-yl)-quinazolin-4-yl)-amine (2.0g) and hydrochloric acid (2N, 50ml) were stirred in THF (20ml) for 16 hr. The resulting precipitate was filtered, washed with water and dried at 60°C *in vacuo* to give the product as a yellow solid (1.80g, 3.73g, 91%); δH [$^2H_6$] -DMSO 12.30 (1H, s), 9.79 (1H, s), 9.62 (1H, s), 8.85 (1H, s), 8.62 (1H, m), 8.31 (1H, s), 8.19 (1H, m), 8.10 (1H, d), 7.90 (2H, m), 7.78 (2H, m), 7.40 (5H, m), 5.80 (2H, s).

Example 18

(S)-1-(5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-pyrrolidine-2-carboxylic acid amide dihydrochloride

5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-furan-2-carbaldehyde_and L-prolinamide were reacted in an analogous manner to Example 10. Purification by silica gel chromatography, eluting with 4-7%MeOH/$CHCl_3$, followed by acidification with ethereal HCl gave the product as a yellow solid (0.075g, 0.122mmol, 29%); δH [$^2H_6$] -DMSO 12.80 (1H, s), 9.79 (1H, s), 8.85 (1H, s), 8.45 (1H, d), 8.38 (1H, s), 8.22 (1H, s), 8.14 (1H, s), 8.06 (1H, d), 7.82 (1H, d), 7.75 (1H, dd), 7.70 (1H, s), 7.50 (1H, d), 7.30 (5H, m), 6.90 (1H, d), 5.72 (2H, s), 4.64 (1H, m), 4.59 (2H, s), 3.50 (2H, m), 1.90 (4H, m); m/z 544 $(M + 1)^+$.

Example 19

(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine dihydrochloride

5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-furan-2-carbaldehyde_and 2-methylsulphonylamine were reacted in an analogous manner to Example 10 to give the title compound; δH [$^2H_6$] -DMSO 12.15 (1H, s), 10.00 (1H, bs), 9.75 (1H, s), 8.88 (1H, s), 8.45 (1H, d), 8.24 (1H, s), 8.16 (1H, s), 8.00 (1H, d), 7.84 (1H, d), 7.77 (1H, dd), 7.39 (1H, d), 7.30 (5H, m), 6.87 (1H, d), 5.72 (2H, s), 4.46 (2H, s), 3.70 (4H, m), 3.15 (3H, s); m/z $(M + 1)^+$ 553.

Example 20

(4-Phenoxy-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)quinazolin-4-yl)-amine hydrochloride

4-Chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)quinazoline was treated with 4-phenoxyaniline according to Procedure A to give the title compound as a yellow solid; δH [$^2H_6$]DMSO 11.78 (1H,bs), 9.45(1H,s), 8.95 (1H,s), 8.60(1H,dd), 8.10 (1H,d), 7.75 (2H,d) 7.45(2H,d), 7.10(5H,m), 2.68(3H,s); m/z ($M+1^+$) 396.

Example 21

(1-(2-Fluorobenzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from 1-(2-fluorobenzyl)-1H-indazol-5-ylamine and 4-chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.70(1H,s), 9.45(1H,s), 8.90(1H,s), 8.60(1H,d), 8.20(1H,s), 8.13(1H,s), 7.85(1H,d), 7.70(1H,d), 7.38(1H,m), 7.24 (1H,m), 7.17 (3H,m), 5.76(2H,s), 2.65 (3H,s); m/z ($M+1^+$) 452.

Example 22

(1-(3-Fluorobenzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from 1-(3-fluorobenzyl)-1H-indazol-5-ylamine and 4-chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.80(1H,s), 9.45(1H,s), 8.90(1H,s), 8.60(1H,d), 8.25(1H,s), 8.13(2H,m), 7.87(1H,d), 7.79(1H,d), 7.39(1H,dd), 7.10(3H,m), 5.75(2H,s), 2.65 (3H,s); m/z ($M+1^+$) 452.

Example 23

(1-Pyridin-2-ylmethyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from (1-pyridin-2-ylmethyl)-1H-indazol-5-ylamine and 4-chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.70(1H,s), 9.46(1H,s), 8.90(1H,s), 8.55(2H,m), 8.24(1H,s), 8.11(2H,m), 7.80(2H,m), 7.69(1H,dd), 7.33(1H,m), 7.10(1H,d), 5.83(2H,s), 2.66 (3H,s); m/z ($M+1^+$) 435.

Example 24

(1-(2,3-Difluorobenzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from 1-(2,3-difluorobenzyl)-1H-indazol-5-ylamine and 4-chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.90(1H,s), 9.47(1H,s), 8.91(1H,s), 8.60(1H,d), 8.25(1H,s), 8.15(2H,m), 7.89(1H,d), 7.72(1H,dd), 7.40(1H,m), 7.18(1H,m), 6.98(1H,m), 5.83(2H,s), 2.67(3H,s); m/z ($M+1^+$) 470.

Example 25

(3-Chloro-4-(2-fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from 3-chloro-4-(2-fluoro-benzyloxy)aniline and 4-chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.64(1H,bs), 9.40(1H,s), 8.97(1H,s), 8.58(1H,d), 8.11(1H,d), 7.94(1H,d), 7.71(1H,dd), 7.63(1H,dd), 7.45(2H,m), 7.30(2H,m), 5.31(2H,s), 2.68(3H,s); m/z ($M+1^+$) 462.

Example 26

(3-Chloro-4-(3-fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from 3-chloro-4-(3-fluoro-benzyloxy)aniline and 4-chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.73(1H,bs), 9.38(1H,s), 8.94(1H,s), 8.57(1H,d), 8.10(1H,d), 7.90(1H,d), 7.65(1H,dd), 7.45(1H,m), 7.30(3H,m), 7.16(1H,m), 5.30(2H,s), 2.65(3H,s); m/z ($M+1^+$) 462.

Example 27

(4-Benzyloxy-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from 4-benzyloxyaniline and 4-chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.73(1H,bs), 9.41(1H,s), 8.90(1H,s), 8.58(1H,d), 8.10(1H,d), 7.65(2H,d), 7.40(5H,m), 7.15(2H,d), 5.19(2H,s), 2.65(3H,s); m/z ($M+1^+$) 410.

Example 28
(4-(2-Fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from 4-(2-fluoro-benzyloxy)aniline and 4-chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.72(1H,bs), 9.41(1H,s), 8.91(1H,s), 8.59(1H,d), 8.10(1H,d), 7.65(3H,m), 7.45(1H,m), 7.25(2H,m), 7.18(2H,d), 5.20(2H,s), 2.65(3H,s); m/z ($M+1^+$) 428.

Example 29
(4-(3-Fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolinyl)-amine hydrochloride

The title compound was prepared according to Procedure A from 4-(3-fluoro-benzyloxy)aniline and 4-chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.71(1H,bs), 9.40(1H,s), 8.90(1H,s), 8.58(1H,d), 8.09(1H,d), 7.66(2H,d), 7.47(1H,m), 7.33(2H,m), 7.15(3H,m), 5.21(2H,s), 2.65(3H,s); m/z ($M+1^+$) 428.

Example 30
(4-Benzenesulphonyl-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from 4-benzenesulphonylaniline and 4-chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.63(1H,bs), 9.42(1H,s), 8.95(1H,s), 8.56(1H,d), 8.10(6H,m), 7.70(4H,m), 2.65(3H,s); m/z ($M+1^+$) 444.

Example 31
(1-(3,5-Difluoro-benzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from 1-(3,5-difluoro-benzyl)-1H-indazol-5-ylamine and 4-chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 12.50(1H,bs), 10.35(1H,s), 9.25(1H,s), 8.61(1H,s),

8.35(1H,m), 8.22(2H,m), 7.88(1H,dd), 7.75(2H,m), 7.16(1H,m), 6.93(1H,m), 5.73(2H,s), 2.67(3H,s); m/z ($M+1^+$) 470.

Example 32

(4-(4-Fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from 4-(4-fluoro-benzyloxy)aniline and 4-chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.68(1H,bs), 9.39(1H,s), 8.89(1H,s), 8.56(1H,d), 8.07(1H,d), 7.64(2H,d), 7.54(2H,m), 7.24(2H,dd), 7.14(2H,d), 5.14(2H,s), 2.65(3H,s); m/z ($M+1^+$) 428.

Example 33

(4-(2-Fluoro-benzyloxy)-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from 4-(2-fluoro-benzyloxy)aniline and 4-chloro-6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.80(1H,bs), 9.54(1H,s), 8.93(1H,s), 8.67(1H,dd), 8.14(1H,d), 7.67(2H,d), 7.59(1H,m), 7.46(1H,m), 7.29(2H,m), 7.19(2H,d), 5.23(2H,s); m/z ($M+1^+$) 482.

Example 34

(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from 4-(3-fluoro-benzyloxy)aniline and 4-chloro-6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.74(1H,bs), 9.51(1H,s), 8.91(1H,s), 8.66(1H,dd), 8.12(1H,d), 7.65(2H,d), 7.48(1H,m), 7.32(2H,m), 7.19(1H,m), 7.17(2H,d), 5.20(2H,s); m/z ($M+1^+$) 482.

Example 35

(4-(4-Fluoro-benzyloxy)-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from 4-(4-fluoro-benzyloxy)aniline and 4-chloro-6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.81(1H,bs), 9.53(1H,s), 8.91(1H,s), 8.67(1H,dd), 8.13(1H,d), 7.63(2H,d), 7.54(2H,dd), 7.25(2H,dd), 7.15(2H,d), 5.15(2H,s); m/z ($M+1^+$) 482.

Example 36

(1-Benzyl-1H-indazol-5-yl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from 1-benzyl-1H-indazol-5-ylamine and 4-chloro-6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.96(1H,bs), 9.58(1H,s), 8.91(1H,s), 8.69(1H,dd), 8.22(1H,s), 8.14(1H,d), 8.10(1H,d), 8.85(1H,d), 8.67(1H,dd), 7.30(5H,m), 5.71(2H,s); m/z ($M+1^+$) 488.

Example 37

(4-Pyridin-3-ylmethoxy)-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

The title compound was prepared according to Procedure A from (4-pyridin-3-ylmethoxy)aniline and 4-chloro-6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.44(1H,bs), 9.50(1H,s), 8.85(2H,m), 8.70(1H,d), 8.62(1H,d), 8.16(1H,d), 8.10(1H,d), 7.69(2H,d), 7.65(1H,m), 7.18(2H,d), 5.29(2H,s); m/z ($M+1^+$) 465.

Example 38

(1-Benzyl-1H-indazol-5-yl)-(6-(3-methyl-3H-imidazol-4-yl)-quinazolin-4-yl)-amine

Prepared in an analogous manner to Example 6 according to Procedure B from (1-Benzyl-1H-indazol-5-yl)-(6-iodoquinazolin-4-yl)-amine and 5-(tributylstannyl)-1-methylimidazole; δH [$^2H_6$]DMSO 9.98(1H,s), 8.62(1H,s), 8.55(1H,s), 8.20(1H,s), 8.15(1H,s), 7.99(1H,dd), 7.83(2H,m), 7.70(2H,m), 7.28(6H,m), 5.70(2H,s), 3.70(3H,s); m/z $(M+1)^+$ 432.

Example 39

(1-Benzyl-1H-indazol-5-yl)-(6-(1-methyl-1H-imidazol-2-yl)quinazolin-4-yl)-amine

Prepared in an analogous manner to Example 6 according to Procedure B from (1-Benzyl-1H-indazol-5-yl)-(6-iodoquinazolinyl)-amine and 2-(tributylstannyl)-1-methylimidazole (prepared according to the published method: J. Organometallic Chem., (1989), 61); δH [$^2H_6$]DMSO 10.09(1H,s), 8.80(1H,s), 8.57(1H,s), 8.20(1H,s), 8.15(2H,m), 7.85(1H,d), 7.70(2H,m), 7.30(6H,m), 7.09(1H,s), 5.70(2H,s), 3.88(3H,s); m/z $(M+1)^+$ 432.

Example 40

(4-Benzyloxy-phenyl)-(6-(1H-tetrazol-5-yl)-quinazolin-4-yl)-amine

(4-Benzyloxy-phenyl)-(6-cyanoquinazolin-4-yl)-amine (0.106g) in dimethylformamide was treated with sodium azide (0.06g) and ammonium chloride (0.05g) and the mixture stirred at 180°C for 18 hours. The mixture was cooled, poured onto water and extracted with ethyl acetate/THF (3:1). The organic extracts were dried and concentrated *in vacuo*. The residue was purified using solid phase extraction to yield the title compound (0.024g); δH [$^2H_6$]DMSO 10.18(1H,s), 9.25(1H,s), 8.55(1H,s), 8.40(1H,d), 7.88(1H,d), 7.74(2H,d), 7.45(6H,m), 7.07(2H,d), 5.17(1H,s); m/z $(M+1)^+$ 396.

Example 41

(1-Benzyl-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine hydrochloride

(1-Benzyl-1H-indazol-5-yl)-(6-hydrazidoquinazolin-4-yl)-amine (0.155g) was treated with triethylorthoacetate (8ml) at reflux for 18 hours. Concentration *in vacuo* and chromatography on silica was followed by precipitation from methanolic HCl to give the title compound as a yellow solid; δH [$^2H_6$]DMSO 11.93(1H,s), 9.50(1H,s), 8.97(1H,s), 8.67(1H,d), 8.30(1H,s), 8.16(2H,m), 7.91(1H,d), 7.74(1H,dd), 7.38(5H,m), 5.80(2H,s), 2.74(3H,s); m/z $(M+1)^+$ 434.

Example 42

(1-Benzyl-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-triazol-2-yl)-quinazolin-4-yl)-amine

(1-Benzyl-1H-indazol-5-yl)-(6-hydrazido-quinazolin-4-yl)-amine (0.102g) in methanol (5ml) under N_2 was treated with ethyl imidate hydrochloride (0.03g) and triethylamine (0.05g) at reflux for 18 hours. The resulting mixture was absorbed onto

silica and chromatographed to give the title compound (0.018g); δH [$^2H_6$]DMSO 10.25(1H,s), 9.20(1H,s), 8.55(1H,s), 8.45(1H,d), 8.22(1H,s), 8.12(2H,s), 7.82(1H,d), 7.73(2H,s), 7.30(5H,m), 5.70(2H,s), 2.50(3H,s); m/z $(M+1)^+$ 433.

Example 43

(S)-1-(2-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-3-methyl-3H-imidazol-4-ylmethyl)-pyrrolidine-2-carboxylic acid amide

2-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-3-methyl-3H-imidazole-4-carbaldehyde was dissolved in dichloromethane (5ml) containing glacial acetic acid (0.03ml). L-prolinamide (0.028g) was added and the mixture stirred at 20°C for 0.75 hours. Sodium acetoxyborohydride (0.08g) was added and the reaction stirred at 20°C for 18 hours. The mixture was partitioned between 2N sodium carbonate and ethyl acetate, the organic phase was dried over magnesium sulphate and concentrated *in vacuo*. Chromatography on silica gave the title compound (0.008g) as a yellow solid; tlc (SiO_2, CH_2Cl_2:EtOH:NH_3, 100:8:1) Rf 0.18; m/z $(M+1)^+$ 534.

Example 44

(1-Benzyl-1H-indazol-5-yl)-(6-(5-methanesulphonylmethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine

(1-Benzyl-1H-indazol-5-yl)-(6-(methanesulphonylethanoyl-hydrazido)-quinazolin-4-yl)-amine (0.06g) was treated with phosphorus oxychloride (0.02ml) in dry acetonitrile (10ml) at reflux under N_2 for 18 hours. Further portions of the chloride were added (2 x.0.1ml and 1 x 0.2ml) over a period of 8 days. Cooling, concentration *in vacuo* and chromatography on silica gave the desired compound after precipitation from methanolic HCl; LC R.T. 3.97 mins., m/z $(M+1)^+$ 434.

Example 45

(4-Benzyloxy-phenyl)-(6-(1-methylpyridinium-2-yl)quinazolin-4-yl)-amine chloride hydrochloride

Methyl iodide (20 drops) was added to a solution of (4-benzyloxy-phenyl)-(6-(pyridin-2-yl)-quinazolin-4-yl)-amine (0.10g, 0.247mmol) and the mixture was stirred at room temperature for 24 hours. As tlc indicated incomplete reaction, further methyl iodide (1.0ml) was added and stirring was continued for 4 days, by which time tlc showed complete reaction. The yellow precipitate was collected by filtration and washed with acetone. It was treated with 2N aqueous HCl, and the deeper yellow solid was

collected by filtration and again washed with acetone to give the product (0.090g, 0.183mmol, 74%); δH [$^2H_6$]DMSO 12.1 (1H,s), 9.62 (1H,s), 8.98 (1H,s), 8.93 (1H,dd), 8.81 (1H,d), 8.43 (1H,d), 8.19 (1H,d), 8.08 (1H,td), 7.64 (2H,d), 7.33-7.58 (6H,m), 7.18 (2H,d), 5.18 (2H,s), 4.09 (3H,s); m/z ($M+1^+$) 419.

Example 46

(4-Benzyloxy-phenyl)-(6-(2,3-dimethyl-3H-imidazol-4-yl)-quinazolin-4-yl)-amine hydrochloride.

The (4-benzyloxy-phenyl)-(6-iodoquinazolin-4-yl)-amine (0.30g, 0.61mmol), 1,2-dimethyl-5-(tributylstannyl)imidazole (Iddon, B. and Lim, B.L., *J. Chem. Soc., Perkin Trans. 1* (1983), (2), 271-7) (0.46g, 1.19mmol) and bis(triphenylphosphine)palladium (II) chloride (0.05g, 0.07mmol) were reacted in dioxane (10ml) according to Procedure B for 18 hours. Purification by silica gel chromatography (eluting with 10%MeOH/EtOAc), followed by acidification with methanolic HCl and trituration with ether gave the product (0.163g, 0.36mmol, 58%); δH [$^2H_6$]DMSO 12.4 (1H,s), 9.52 (1H,s), 8.91 (1H,s), 8.22 (1H,d), 8.15 (1H,d), 8.03 (1H,s), 7.70 (2H,d), 7.30-7.60 (5H,m), 7.13 (2H,d), 5.17 (2H,s), 3.73 (3H,s), 2.57 (3H,s); m/z ($M+1^+$) 422.

Example 47

(4-Benzyloxy-phenyl)-(-6-(3-methylisoxazol-5-yl)-quinazolin-4-yl)-amine hydrochloride

A stirred mixture of (4-benzyloxy-phenyl)-(6-ethynylquinazolin-4-yl)-amine (0.20g, 0.57mmol), nitroethane (0.20g, 2.7mmol), phenylisocyanate (0.15ml, 0.164g, 1.38mmol), and triethylamine (3 drops) in a mixture of ethyl acetate (10ml) and dichloromethane (5ml) was heated at reflux for 18 hours. After cooling the mixture was filtered to remove solid, and the concentrated filtrate was purified by silica gel chromatography, eluting with 50% ethyl acetate/*i*-hexane. After concentration of the appropriate fractions, the material obtained was treated with methanolic HCl, the solvent was removed *in vacuo* and the residue was triturated with ether to give the title compound as a yellow solid (0.027g, 0.061mmol, 11%); δH [$^2H_6$]DMSO 12.0 (1H,s), 9.55 (1H,s), 8.91 (1H,s), 8.48 (1H,d), 8.03 (1H,d), 7.68 (2H,d), 7.32-7.55 (5H,m), 7.22 (1H,s), 7.15 (2H,d), 5.18 (2H,s), 2.35 (3H,s); m/z ($M+1^+$) 409.

Example 48

(4-Benzyloxy-phenyl)-(6-(5-(((2-methanesulphonyl-ethyl)-methyl-amino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine

In an analogous manner to Example 10, 5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride (0.217g, 0.474mmol) was reacted with *N*-methyl-*N*-(2-methanesulphonyl-ethyl)amine (0.411g, 3.0mmol). Purification by silica gel chromatography, eluting with 2-3% MeOH/$CHCl_3$, followed by trituration with ether, gave the title compound as a pale yellow solid (0.100g, 0.184mmol, 39%); δH [$^2H_6$]DMSO 9.84 (1H,s), 8.63 (1H,s), 8.48 (1H,s), 8.12 (1H,d), 7.78 (1H,d), 7.68 (2H,d), 7.13-7.52 (5H,m), 7.02-7.10 (3H,m), 6.55 (1H,d), 5.14 (2H,s), 3.70 (2H,s), 3.35-3.44 (2H, obscured by water), 3.05 (3H,s), 2.84 (2H,t), 2.28 (3H,s).

Example 49

N-(2-((5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-amino)-ethyl)-methanesulphonamide dihydrochloride

In an analogous manner to Example 10, 5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride (0.200g, 0.436mmol) was reacted with 2-(methanesulphonamido)ethylamine (0.350g, 2.53mmol). On completion of the reaction the mixture was acidified with dilute HCl and diluted with water, but no solid was formed. The mixture was concentrated *in vacuo*, and the residue was washed with acetone, 2N HCl and acetone again, and dried at 60°C *in vacuo* to give the title compound as a yellow solid (0.210g, 0.340mmol, 78%); δH [$^2H_6$]DMSO 12.01 (1H,s), 9.82 (1H, br s), 9.77 (1H,s), 8.88 (1H,s), 8.40 (1H,d), 8.02 (1H,d), 7.76 (2H,d), 7.31-7.53 (6H,m), 7.14 (2H,d), 6.84 (1H,d), 5.18 (2H,s), 4.40 (2H,s), 3.34-3.48 (2H, m), 3.08-3.18 (2H,m), 2.96 (3H,s); m/z ($M+1^+$) 544.

Example 50

2-((5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-amino)-ethanesulphonic acid amide

In an analogous manner to Example 10, 5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride (0.200g, 0.436mmol) was reacted with 2-aminoethylsulphonamide hydrochloride (0.200g, 1.245mmol) and triethylamine (10 drops). On completion of the reaction, the mixture was acidified with dilute HCl and diluted with water, to give the crude product as a precipitate collected by filtration. Treatment with triethylamine followed by purification by silica gel chromatography,

eluting with 3-10% MeOH/$CHCl_3$ gave the title compound as a yellow solid (0.085g, 0.160mmol, 37%); δH [$^2H_6$]DMSO 9.61 (2H, br s), 9.25 (1H,s), 8.58 (1H,s), 8.23 (1H,d), 7.77-7.88 (3H,m), 7.30-7.52 (5H,m), 7.26 (2H,s), 7.20 (1H,d), 7.08 (2H,d), 6.81 (1H,d), 5.14 (2H,s), 4.44 (2H,s), 3.34-3.60 (2H, m), 3.25-3.45 (2H,obscured by water); m/z ($M+1^+$) 530.

Example 51

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carboxylic acid methyl ester

(4-Benzyloxy-phenyl)-(6-(5-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-furan-2-yl)-quinazolin-4-yl)-amine (0.680g, 1.30mmol) was dissolved in THF (10ml) and 2N aqueous HCl (10ml) was added. The mixture was stirred at room temperature for 2 hours. The THF was removed *in vacuo* and the residue diluted with water to preciptate the intermediate (partial hydrolysis) 5-(4-(4-benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carboxylic acid (3-methyloxetan-3-yl)-methyl ester which was collected by filtration and washed with water and acetone; δH [$^2H_6$]DMSO 12.10 (1H,s), 9.50 (1H,s), 8.87 (1H,s), 8.43 (1H,s), 8.00 (1H,s), 7.66 (2H,d), 7.58 (1H,d), 7.30-7.54 (6H,m), 7.13 (2H,d), 5.16 (2H,s), 4.14 (2H,s), 3.28-3.41 (4H,m), 0.88 (3H,s). This solid was suspended in a mixture of MeOH (15ml) and NaOH (2N, 15ml), and the mixture was stirred at room temperature for 2 hours. The reaction was diluted with water to give the title product as a yellow solid, which was collected by filtration (0.375g, 0.831mmol, 64%); δH [$^2H_6$]DMSO 10.06 (1H,s), 8.91 (1H,s), 8.48 (1H,s), 8.21 (1H,d), 7.80 (1H,d), 7.63 (2H,d), 7.25-7.52 (7H,m), 7.05 (2H,d), 5.10 (2H,s), 3.85 (3H,s); m/z ($M+1^+$) 452.

Example 52

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carboxylic acid hydrochloride

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carboxylic acid methyl ester (0.150g, 0.332mmol) was suspended in a mixture of EtOH (2ml) and 2N aqueous NaOH (2ml). The mixture was stirred at room temperature for 15mins. To facilitate dissolution, $CHCl_3$ (2ml) was added and stirring was continued for 3 days, by which time tlc showed there to be no remaining starting material. The organic solvents were removed *in vacuo* and the residue diluted with water and treated with 2N aqueous HCl to give the product as a yellow solid, which was collected by filtration (0.130g, 0.274mmol, 83%); m/z ($M+1^+$) 438.

Example 53

5-[4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl]-furan-2-carboxylic acid (2-methanesulphonyl-ethyl)-amide hydrochloride

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carboxylic acid hydrochloride (0.130g, 0.274mmol) and carbonyldiimidazole (0.053g, 0.326mmol) were mixed in THF (2ml) and stirred at room temperature under a nitrogen atmosphere for 2.5 hours. 2-(Methylsulphonyl)ethylamine hydrochloride (0.055g, 0.45mmol) and triethylamine (5 drops) were added, and the resulting mixture was stirred at room temperature for 3 days. The mixture was diluted with water, and treated with conc. HCl until at pH 1, to give the crude product as a yellow solid, which was further purified by silica gel chromatography, eluting with 5-10% MeOH/$CHCl_3$. Concentration of the relevant fractions, followed by treatment with 2N aqueous HCl gave the product as an yellow solid, which was collected by filtration and washed with acetone and ether (0.028g, 0.048mmol, 18%); δH [$^2H_6$]DMSO 12.05 (1H,s), 9.66 (1H,s), 9.21 (1H,t), 8.88 (1H,s), 8.55 (1H,d), 7.91 (1H,d), 7.71 (2H,d), 7.28-7.54 (7H,m), 7.15 (2H,d), 5.18 (2H,s), 3.72 (2H,dd), 3.40-3.52 (2H obscured by water signal), 3.07 (3H,s); m/z ($M+1^+$) 543.

Example 54

2-((5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-amino)-ethanesulphonic acid methylamide

In an analogous manner to Example 10, 5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride (0.200g, 0.436mmol) was reacted with 2-(methylsulphonamido)ethylamine (Int. J. Pept. Protein Res., (1984), 24(4), 367-76) (0.200g, 1.145mmol) and triethylamine (10 drops). On completion of the reaction the mixture was diluted with water and acidified with dilute HCl and the resulting solid collected. Treatment with triethylamine followed by purification by silica gel chromatography, eluting with 4-6% MeOH/$CHCl_3$, gave the title compound as a yellow solid (0.080g, 0.147mmol, 34%); δH [$^2H_6$]DMSO 9.85 (1H,s), 8.74 (1H,s), 8.48 (1H,s), 8.14 (1H,d), 7.75 (1H,d), 7.65 (2H,d), 7.33-7.54 (5H,m), 7.02-7.12 (3H,m), 6.91 (1H,br), 6.49 (1H,d), 5.14 (2H,s), 3.84 (2H,s), 3.20 (2H,t), 2.88-2.98 (2H, m), 2.53-2.60 (3H,m, obscured by DMSO); m/z ($M+1^+$) 544.

Example 55

(1-Benzyl-1H-indazol-5-yl)-(6-(3-methyl-1,2,4-oxadiazol-5-yl)-quinazolin-4-yl)-amine hydrochloride

(4-(1-Benzyl-1H-indazol-5-yl)-quinazolin-6-yl)-carboxylic acid (0.150g, 0.379mmol) was stirred with 1,1'-carbonyldiimidazole (0.123g, 0.759mmol) in dry THF at room temperature for 3 hours. Acetamidoxime (0.084g, 1.13mmol) was added and the mixture was stirred at room temperature overnight. The mixture was partitioned between water and ethyl acetate, and the organic extracts were dried and concentrated. Purification by silica gel chromatography, eluting with 100:8:1 dichloromethane:EtOH:NH_3, gave a pale yellow gum. Treatment with methanolic HCl, followed by concentration *in vacuo* gave the product as a bright yellow solid (0.038g, 0.081mmol, 21%); δH [$^2H_6$]DMSO 9.62 (1H,s), 8.95 (1H,s), 8.69 (1H,d), 8.23 (1H,d), 8.08-8.15 (2H,m), 7.85 (1H,d), 7.67 (1H, dd), 7.23-7.39 (5H,m), 5.72 (2H,s), 3.40-3.60 (3H,s, obscured by water); m/z ($M+1^+$) 434.

Example 56

(4-Benzyloxy-phenyl)-(6-(5-methyl-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine

(4-(4-Benzyloxyanilino)quinazolin-6-yl)-(*N*-hydroxycarboximidamide) (0.077g, 0.20mmol) and ethyl acetate (0.02ml, 0.018g, 0.20mmol) were reacted according to Procedure C to give the product as a cream solid (0.020g, 0.049mmol, 24%); δH $CDCl_3$ 8.76 (1H,s), 8.62 (1H,s), 8.45 (1H,dd), 7.98 (1H,d), 7.57-7.65 (3H,m), 7.30-7.50 (5H,m), 7.05 (2H,d), 5.09 (2H,s), 2.71 (3H,s); m/z ($M+1^+$) 410.

Example 57

(4-Benzyloxy-phenyl)-(6-(5-(2-dimethylamino-ethyl)-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine

(4-(4-Benzyloxyanilino)quinazolin-6-yl)-(*N*-hydroxycarboximidamide) (0.20mmol) and methyl 3-(dimethylamino)propionate (0.20mmol) were reacted according to Procedure C to give the product as a cream solid (0.035g, 0.075mmol, 38%); δH [$^2H_6$]DMSO 10.22 (1H,s), 9.22 (1H,s), 8.57 (1H,s), 8.37 (1H,dd), 7.89 (1H,d), 7.69 (2H,d), 7.32-7.52 (5H,m), 7.07 (2H,d), 5.14 (2H,s), 3.21 (2H,t), 2.79 (2H,t), 2.20 (6H,s); m/z ($M+1^+$) 467.

Example 58

(4-Benzyloxy-phenyl)-(6-(5-(dimethylaminomethyl)-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine

((4-Benzyloxy-phenyl)-quinazolin-6-yl)-(*N*-hydroxycarboximidamide) (0.20mmol) and *N,N*-dimethylglycine methyl ester (0.20mmol) were reacted according to Procedure C, followed by acidification with a solution of HCl in dioxane, to give the product as a yellow solid; δH [$^2H_6$]DMSO 9.51 (1H,s), 8.91 (1H,s), 8.63 (1H,d), 8.12 (1H,d), 7.64 (2H,d), 7.39-7.54 (5H,m), 7.16 (2H,d), 5.18 (2H,s), 3.02 (2H,s), 2.20 (6H,s); m/z ($M+1^+$) 453.

Example 59

(1-Benzyl-1H-indazol-5-yl)-(6-(5-(((2-methanesulphonyl-ethyl)-amino)-methyl)-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine

(4-(1-Benzyl-1H-indazol-5-yl)-quinazolin-6-yl)-(*N*-hydroxycarboximidamide) (0.123g, 0.30mmol) and *N*-(ethoxycarbonylmethyl)-*N*-(2-methylsulphonylethyl) trifluoroacetamide (0.183g, 0.60mmol) were reacted according to Procedure C. After being left overnight the reaction had not gone to completion so further sodium hydride (60% dispersion on mineral oil, 0.013g, 0.33mmol) and ester (0.183g, 0.60mmol) were added and the reaction was stirred for a further 24 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica gel chromatography, eluting with 10% MeOH/$CHCl_3$ to give the title compound as a yellow solid (0.028g,0.050mmol, 17%); δH [$^2H_6$]DMSO 10.39 (1H,s), 9.30 (1H,s), 8.59 (1H,s), 8.40 (1H,d), 8.11-8.22 (2H,m), 7.91 (1H,d), 7.72 (2H,m), 7.22-7.38 (5H,m), 5.68 (2H,s), 4.20 (2H,s), 3.28-3.38 (2H, obscured by water), 3.08 (2H,t), 3.05 (3H,s); m/z ($M+1^+$) 555.

Example 60

(1-Benzyl-1H-indazol-5-yl)-(6-(5-methanesulphonylmethyl-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine

(4-(1-Benzyl-1H-indazol-5-yl)-quinazolin-6-yl)-(*N*-hydroxycarboximidamide) (0.30mmol) and ethyl 2-(methylsulphonyl)acetate (0.60mmol) were reacted according to Procedure C to give the product as a yellow solid (0.030g,0.059mmol, 20%); δH [$^2H_6$]DMSO 10.41 (1H,s), 9.30 (1H,s), 8.60 (1H,s), 8.42 (1H,dd), 8.13-8.21 (2H,m), 7.94 (1H,d), 7.69-7.76 (2H,m), 7.21-7.38 (5H,m), 5.69 (2H,s), 5.35 (2H,s), 3.30 (3H,s); m/z ($M+1^+$) 512.

Example 61

(1-Benzyl-1H-indazol-5-yl)-(6-(5-methyl-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl0-amine

(4-(1-Benzyl-1H-indazol-5-yl)-quinazolin-6-yl)-(*N*-hydroxycarboximidamide) (0.30mmol) and ethyl acetate were reacted according to Procedure C to give the product as a yellow solid (0.065g,0.150mmol, 50%); δH [$^2H_6$]DMSO 10.38 (1H,s), 9.28 (1H,d), 8.59 (1H,s), 8.38 (1H,dd), 8.21 (1H,s), 8.14 (1H,s), 7.90 (1H,d), 7.72 (2H,s), 7.22-7.38 (5H,m), 5.68 (2H,s), 2.73 (3H,s); m/z ($M+1^+$) 434.

Example 62

(1-Benzyl-1H-indazol-5-yl)-6-(5-(pyridin-3-ylmethyl)-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine

(4-(1-Benzyl-1H-indazol-5-yl)-quinazolin-6-yl)-(*N*-hydroxycarboximidamide) (0.30mmol) and methyl 3-pyridineacetate (available from Salor) were reacted according to Procedure C to give the product as a yellow solid (0.028g,0.055mmol, 18%); δH [$^2H_6$]DMSO 10.38 (1H,s), 9.26 (1H,s), 8.70 (1H,s), 8.54-8.60 (2H,m), 8.37 (1H,d), 8.14-8.20 (2H,m), 7.86-7.94 (2H,m), 7.68-7.77 (2H,m), 7.42-7.50 (1H,m), 7.20-7.38 (5H,m), 5.69 (2H,s), 4.59 (2H,s); m/z ($M+1^+$) 511.

Example 63

(1-Benzyl-1H-indazol-5-yl)-(6-(1-methylpyrrol-2-yl)-quinazolin-4-yl)-amine hydrochloride

A stirred solution of 1-methyl-2-(tri-*n*-butylstannyl)pyrrole (prepared as described in H.M.R. Hoffmann et al. Synthesis, 1996, 164) (1.07g, 2.89mmol), (1-benzylindazol-5-yl)-(6-iodoquinazolin-4-yl)-amine hydrochloride (1.0g, 1.95mmol), triethylamine (0.4ml, 0.29g, 2.87mmol) and 1,4-bis(diphenylphosphino)-butane palladium (II) chloride (0.1g, catalytic) in dioxane (10ml) was heated to reflux under a nitrogen atmosphere for 18 hours. The mixture was concentrated *in vacuo* and purified by silica gel chromatography, eluting with 2:1 *i*-hexane/EtOAc. Concentration of the appropriate fractions gave a yellow solid which was dissolved in EtOAc and treated with a solution of HCl in dioxane. The precipitate was collected by filtration, washed with EtOAc and dried at 60C *in vacuo* to give the product as a green-yellow solid (0.26g, 0.557mmol, 29%) ; δH [$^2H_6$]DMSO 11.95 (1H,s), 8.86-8.96 (2H,m), 8.18-8.27 (2H,m), 8.07 (1H,s), 7.99 (1H,d), 7.83 (1H,d), 7.65 (1H,dd), 7.22-7.40 (5H,m), 7.01 (1H,t), 6.49 (1H,dd), 6.19 (1H,t), 5.71 (2H,s), 3.82 (3H,s); m/z ($M+1^+$) 431.

Example 64

5-(4-(1-Benzyl-1H-indazol-5-yl)-quinazolin-6-yl)-1-methyl-pyrrole-2-carbaldehyde

A stirred solution of 5-formyl-1-methyl-2-(tri-*n*-butylstannyl)pyrrole (prepared as described in F. Denat et al. J. Organometallic Chem., 423, 173,(1992)) (1.60g, 4.02mmol), (1-benzyl-1H-indazol-5-yl)-(6-iodoquinazolin-4-yl)-amine hydrochloride (1.0g, 1.95mmol), triethylamine (0.3ml, 0.218g, 2.2mmol) and 1,4-bis(diphenylphosphino)-butane palladium (II) chloride (0.2g, catalytic) in dioxane (20ml) was heated to reflux under a nitrogen atmosphere for 18 hours (Procedure B). The mixture was concentrated *in vacuo* and purified by silica gel chromatography, eluting with 60%-100% EtOAc/*i*-hexane. Concentration of the appropriate fractions gave the product as a yellow solid (0.460g, 1.00mmol, 51%); δH [$^2H_6$]DMSO 10.00 (1H,s), 9.64 (1H,s), 8.73 (1H,s), 8.59 (1H,s), 8.22 (1H,s), 8.13-8.16 (1H,m), 8.01 (1H,dd), 7.86 (1H,d), 7.68-7.75 (2H,m), 7.19-7.37 (6H,m), 6.59 (1H,d), 5.68 (2H,s), 3.98 (3H,s); m/z ($M+1^+$) 459.

Example 65

1-(3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-1,2,4-oxadiazol-5-ylmethyl)-piperidin-4-one

(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-(*N*-hydroxycarboximidamide) (0.30mmol) and methyl 2-(4-piperidon-1-yl)acetate were reacted according to Procedure C to give the product as a yellow solid (0.035g,0.066mmol, 22%); δH [$^2H_6$]DMSO 10.39 (1H,s), 9.28 (1H,d), 8.57 (1H,s), 8.39 (1H,d), 8.10-8.22 (2H,m), 7.91 (1H,d), 7.67-7.74 (2H,m), 7.21-7.37 (5H,m), 5.67 (2H,s), 4.20 (2H,s), 3.27-3.62 (4H,m, obscured by water), 2.82-2.99 (4H,m); m/z ($M+1^+$) 531.

Example 66

1-(3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-1,2,4-oxadiazol-5-ylmethyl)-pyrrolidin-2-one

(4-(1-Benzylindazol-5-ylamino)-quinazolin-6-yl)-(*N*-hydroxycarboximidamide) (0.30mmol) and ethyl 2-(pyrrolidin-2-on-1-yl)acetate (Aldrich) were reacted according to Procedure C to give the product as a yellow solid (0.072g,0.139mmol, 46%); δH [$^2H_6$]DMSO 10.30 (1H,s), 9.27 (1H,d), 8.59 (1H,s), 8.39 (1H,dd), 8.15-8.20 (2H,m), 7.91 (1H,d), 7.70-7.74 (2H,m), 7.22-7.37 (5H,m), 5.69 (2H,s), 4.88 (2H,s), 3.55 (2H,t), 2.35 (2H,t), 2.00-2.11 (2H,m); m/z ($M+1^+$) 517.

Example 67

1-(3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-1,2,4-oxadiazol-5-ylmethyl)-imidazolidin-2,5-dione

(4-(1-Benzyl-1H-indazol-5-ylamino)quinazolin-6-yl)-(*N*-hydroxycarboximidamide) (0.30mmol) and methyl 2-(2,5-dioxo-imidazolidin-1-yl)acetate (Tarlton and McKay, Can. J. Chem., 36 (1958), 496) were reacted according to Procedure C to give the product as a yellow solid (0.097g,0.182mmol, 61%); δH [$^2H_6$]DMSO 10.41 (1H,s), 9.25 (1H,s), 8.58 (1H,s), 8.31-8.41 (2H,m), 8.12-8.19 (2H,m), 7.90 (1H,d), 7.70-7.73 (2H,m), 7.21-7.38 (5H,m), 5.68 (2H,s), 5.04 (2H,s), 4.11 (2H,s); m/z ($M+1^+$) 532.

Example 68

3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-4H-1,2,4-oxadiazolidin-3-one

Carbonyl diimidazole (0.054g, 0.33mmol) was added to a solution of 4-(1-benzylindazol-5-yl)quinazolin-6-yl-(*N*-hydroxycarboximidamide) (0.123g, 0.30mmol) in dry THF (10ml) under a nitrogen atmosphere, and the mixture was stirred at room temperature overnight. LC/MS showed complete disappearance of the starting material, so the mixture was treated with 1,5-diazabicyclo[4.3.0]non-5-ene (0.148g, 1.2mmol) and the mixture stirred for 20 hours. Concentration *in vacuo*, and chromatography on silica using a Bond Elut ™ cartridge, eluting with $CHCl_3$ then a gradient of 2%-5% MeOH/$CHCl_3$, gave the product as a yellow solid (0.027g, 0.062mmol, 21%); δH [$^2H_6$]DMSO 10.25 (1H,br s), 9.08 (1H,s), 8.58 (1H,s), 8.12-8.23 (3H,m), 7.88 (1H,d), 7.71 (2H,s), 7.17-7.38 (5H,m), 5.68 (2H,s); m/z ($M+1^+$) 436.

Example 69

(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesuphonyl-ethyl-amino)-methyl)-1-methyl-pyrrol-2-yl)-quinazolin-4-yl)-amine hydrochloride

5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-furan-2-carbaldehyde (0.10g, 0.22mmol) was strirred with 2-(methylsulphonyl)ethylamine (0.10g, 0.81mmol) and molecular sieves in dry dichloromethane (2ml) for 30 min under a nitrogen atmosphere. Sodium triacetoxyborohydride (0.17g, 0.80mmol) and glacial acetic acid (2 drops) were added and the mixture was stirred at room temperature for 5 hours. The solution was decanted, washed with 8% aq. $NaHCO_3$, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with 10% MeOH/EtOAc. Concentration of the appropriate fractions gave the

free base of the product as a yellow solid, which was redissolved in EtOAc and treated with ethereal HCl. This mixture was concentrated *in vacuo* to give the title compound as a yellow solid (0.066g, 0.103mmol, 47%); δH [$^2H_6$]DMSO 12.15 (1H,s), 9.71 (2H,br s), 9.02 (1H,s), 8.89 (1H,s), 8.22 (1H,s), 8.16 (1H,d), 8.02-8.09 (2H,m), 7.83 (1H,d), 7.67 (1H,dd), 7.22-7.39 (5H,m), 6.51 (2H,s), 5.72 (2H,s), 4.38 (2H,s,) 3.81 (3H,s), 3.65-3.75 (2H,m), 3.38-3.50 (2H,m), 3.15 (3H,s); m/z ($M+1^+$) 566.

Example 70

(4-Benzyloxy-phenyl)-(6-(1-(3-N,N-dimethylaminopropyl)-imidazol-5-yl)- quinazolin-4-yl)-amine

1-(3-N,N-Dimethylaminopropyl)-5-tri-n-butylstannylimidazole (0.44g) was treated with (4-benzyloxy-phenyl)-(6-iodoquinazolin-4-yl)amine (0.3g) and silver (I) oxide (0.085g), 1,4-bis(diphenylphosphino)butane palladium (II) chloride (37mg) in dioxane (10ml) at 90°C under nitrogen for 60 hours. The cooled mixture was absorbed onto silica and purified by chromatography to give the title product (0.10g); δH ($^2H_6$ DMSO) 9.80 (1H,s), 8.62 (1H,s), 8.57 (1H,s), 7.95 (1H,d), 7.85 (2H,d), 7.72 (2H,d), 7.45 (5H,m), 7.19 (1H,s), 7.10 (2H,d), 5.15 (2H,s), 4.22 (2H,t), 2.06 (2H,t), 2.01 (6H,s), 1.65 (2H,m); m/z $(m+1)^+$ 479.

Example 71

(1-Benzyl-1H-indazolyl)-(6-(1-(3-N,N-dimethylaminopropyl)-imidazol-5-yl)-quinazolin-4-yl)-amine

Prepared via an analogous procedure to Example 70 from (1-Benzyl-1H-indazolyl)-(6-iodoquinazolin-4-yl)-amine and 1-(3-N,N-dimethylaminopropyl)-5-tri-n-butylstannylimidazole; δH ($^2H_6$ DMSO) 9.90 (1H,s), 8.60(1H,s), 8.52 (1H,s), 8.17 (1H,s), 8.10 (1H,s), 7.90 (2H,d), 7.80 (2H,m), 7.65 (2H,m), 7.24 (5H,m), 7.12 (1H,s), 5.61 (2H,s), 4.14 (2H,t), 1.95 (2H,t), 1.90 (6H,s), 1.58 (2H,m); m/z $(m+1)^+$ 503.

Example 72

(4-Benzyloxy-phenyl)-(6-(1-(3-N,N-dimethylaminopropyl)-imidazol-2-yl)-quinazolin-4-yl)-amine

1-(N,N-Dimethylaminopropyl)-2-tri-n-butylstannylimidazole was treated with (4-benzyloxy-phenyl)-(6-iodoquinazolin-4-yl)amine as described above in Example 70

to give the title product; δH ($^2H_6$ DMSO) 9.90 (1H,s), 8.73 (1H,s), 8.54 (1H,s), 8.01 (1H,d), 7.82 (1H,d), 7.69 (2H,d), 7.40 (6H,m), 7.06 (3H,m), 5.12 (2H,s), 4.08 (2H,t), 2.57 (2H,m), 2.48 (6H,s), 1.93 (2H,m); m/z $(m+1)^+$ 479.

Example 73
(1-Benzyl-1H-indazolyl)-(6-(1-(3-N,N-dimethylaminopropyl)-imidazol-5-yl)-quinazolin-4-yl)-amine
Prepared via an analogous procedure to Example 72 from (1-benzyl-1H-indazolyl)-(6-iodoquinazolin-4-yl)-amine and 1-(3-N,N-dimethylaminopropyl)-2-tri-n-butylstannylimidazole; δH ($^2H_6$ DMSO) 9.90 (1H,s), 8.88(1H,s), 8.67 (1H,s), 8.41 (1H,s), 8.31 (1H,s),8.23 (1H,s), 8.15 (1H,d), 7.94 (1H,d), 7.80 (2H,m), 7.51 (1H,s), 7.48 (5H,m), 7.20 (1H,s), 5.77 (2H,s), 4.25 (2H,t), 2.14 (2H,t), 2.07 (6H,s), 1.86 (2H,m); m/z $(m+1)^+$ 503.

Example 74
(4-Benzyloxy-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine
The title compound was prepared according to Procedure A from 4-benzyloxyaniline and 4-chloro-6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.69(1H,bs), 9.53(1H,s), 8.91(1H,s), 8.65(1H,dd), 8.11(1H,d), 7.64(2H,d), 7.45(5H,m), 7.15(2H,d), 5.19(2H,s); m/z $(M+1^+)$ 464.

Example 75
(1-(2-Fluoro-benzyl)-1H-indazol-5-yl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine
The title compound was prepared according to Procedure A from 1-(2-fluoro-benzyl)-1H-indazol-5-ylamine and 4-chloro-6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.79(1H,bs), 9.53(1H,s), 8.89(1H,s), 8.77(1H,dd), 8.21(1H,s), 8.11(1H,m), 8.10(1H,d), 7.84(1H,d), 7.70(1H,dd), 7.37(1H,m), 7.24 (1H,m), 7.18 (2H,m), 5.76(2H,s); m/z $(M+1^+)$ 506.

Example 76
(1-(3-Fluoro-benzyl)-1H-indazol-5-yl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine

The title compound was prepared according to Procedure A from 1-(3-fluoro-benzyl)-1H-indazol-5-ylamine and 4-chloro-6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.84(1H,bs), 9.54(1H,s), 8.89(1H,s), 8.77(1H,dd), 8.25(1H,s), 8.11(2H,m), 7.87(1H,d), 7.69(1H,dd), 7.39(1H,m), 7.10 (3H,m), 5.73(2H,s); m/z ($M+1^+$) 506.

Example 77

(1-(4-Fluoro-benzyl)-1H-indazol-5-yl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine

The title compound was prepared according to Procedure A from 1-(4-fluoro-benzyl)-1H-indazol-5-ylamine and 4-chloro-6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazoline; δH [$^2H_6$]DMSO 11.91(1H,bs), 9.55(1H,s), 8.91(1H,s), 8.69(1H,dd), 8.23(1H,s), 8.14(2H,m), 7.88(1H,d), 7.69(1H,dd), 7.36(2H,m), 7.18 (2H,dd), 5.71(2H,s); m/z ($M+1^+$) 506

Example 78

(1-Benzyl-1H-indazol-5-yl)-(7-(5-methyl-[1,3,4]oxadiazol-2-yl)-quinazolin-4-yl)- amine hydrochloride

The crude solid 4-Chloro-7-(5-Methyl-[1,3,4]oxadiazol-2-yl)-quinazoline was suspended in dry acetonitrile. 1-Benzyl-1H-indazol-5-ylamine (0.03g) was added and the mixture heated at reflux for 18 hours under nitrogen (Procedure A). The mixture was cooled and the title compound collected by filtration; δH [$^2H_6$]DMSO 11.82(1H,bs), 9.08(1H,s), 8.99(1H,s), 8.47(1H,s), 8.44(1H,d), 8.37(1H,s), 8.17(1H,s), 7.89(1H,d), 7.72(1H,d), 7.35(5H,m), 5.80(2H,s) 2.72 (3H,s); m/z (M+1+) 434.

Example 79

(1-Benzyl-1H-indazol-5-yl)-(7-(3-methyl-3H-imidazol-4-yl)quinazolin-4-yl)- amine

Prepared according to Procedure B from (1-benzyl-1H-indazol-5-yl)-(7-iodoquinazolin-4-yl)-amine hydrochloride and (3-methyl-3H-imidazol-4-yl) tri-n-butylstannane; δH [$^2H_6$] DMSO 11.85(1H,bs), 9.25(1H,s), 9.19(1H,s), 9.02(1H,d), 8.93(1H,s), 8.16(2H,d), 8.06(2H,d), 7.78(1H,d), 7.61(1H,dd), 7.22(5H,m), 5.66(2H,s) 3.92 (3H,s); m/z (M+1+) 432.

Example 80

(1-Benzyl-1H-indazol-5-yl)-[7-(furan-2-yl)-quinazolin-4-yl]-amine hydrochloride

Prepared according to Procedure B from (1-benzyl-1H-indazol-5-yl)-(7-iodoquinazolin-4-yl)-amine hydrochloride and (furan-2-yl)-tri-n-butylstannane; δH [$^2H_6$] DMSO 9.94(1H,bs), 8.61(1H,d), 8.55(1H,s), 8.21(2H,d), 8.00(3H,m), 7.73(2H,s), 7.30(6H,s), 6.74(1H,s), 5.72(2H,s); m/z (M+1+) 418.

Example 81

(1-Benzyl-1H-indazol-5-yl)-[7-(5-(1,3-dioxolan-2-yl)-furan-2-yl)quinazolin-4-yl] amine hydrochloride

Prepared according to Procedure B from (1-benzyl-1H-indazol-5-yl)-(7-iodoquinazolin-4-yl)-amine hydrochloride and 5-(1,3-dioxolan-2-yl)-2-(tri-n-butylstannyl)furan; tlc Rf, 0.25 (100% EtOAc on silica); m/z (M+1+) 490.

Example 82

5-[4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-7-yl]-furan-2-carbaldehyde

(1-Benzyl-1H-indazol-5-yl)-[7-(5-(1,3-dioxolan-2-yl)furan-2-yl)quinazolin-4-yl]-amine hydrochloride (0.27g) was stirred in THF:2N HCl (2:1, 15ml) at 20°C for 1 hour. Filtration gave 5-[4-(1-benzyl-1H-indazol-5-ylamino)-quinazolin-7-yl]-furan-2-carbaldehyde, used directly in the subsequent synthetic step.

Example 83

(1-Benzyl-1H-indazol-5-yl)-[7-{5-[(2-methanesulphonyl-ethylamino)-methyl]-furan-2-yl}-quinazolin-4-yl]-amine

Prepared by an analogous method to Example 10 from 5-[4-(1-benzyl-1H-indazol-5-ylamino)-quinazolin-7-yl]-furan-2-carbaldehyde and 2-methanesulphonylethylamine; δH [$^2H_6$] DMSO 9.92(1H,bs), 8.60(1H,d), 8.55(1H,s), 8.25(1H,s), 8.17(1H,s), 8.00(2H,m), 7.72(2H,m), 7.30(6H,m), 6.53 (1H,d), 5.72(2H,s) 4.55 (1H,m), 3.87 (2H,m), 3.35 (2H,m), 3.08 (3H,s), 3.04 (2H,m); m/z (M+1+) 553.

Example 84

(S)-1-{5-[4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-7-yl]-furan-2-yl-methyl}-pyrrolidine-2-carboxylic acid amide

Prepared by an analogous method to Example 10 from 5-[4-(1-benzyl-1H-indazol-5-yl)-quinazolin-7-yl]-furan-2-carbaldehyde and S-(-)-prolineamide; δH [$^2H_6$] DMSO 9.83(1H,bs), 8.50(1H,d), 8.47(1H,s), 8.15(1H,s), 8.08(1H,s), 7.90(2H,m),

7.65(2H,m), 7.20(6H,m), 7.05 (1H,m), 6.48 (1H,d), 5.62(2H,s) 3.80 (1H,d), 3.70 (1H,d), 3.70 (2H,s), 3.03 (2H,m), 2.00 (1H,m), 1.70 (3H,m); m/z (M+1+) 544.

Example 85

(4-Benzyloxy-phenyl)-(6-(3-methyl-[1,2]oxazol-4-yl)-quinazolin-4-yl)-amine

(4-Benzyloxy-phenyl)-(6-iodoquinazolin-4-yl)-amine hydrochloride (0.35g) in dioxan (10ml) under nitrogen was treated with 4-tributylstannyl-3-methylisoxazole (prepapred according to the literature method: Heterocycles, (1996), 43(6), 1301-1304) (0.4g), silver oxide (0.092g), triethylamine (0.1ml) and [1.4-bis(diphenylphosphino)butane] palladium (II) chloride (0.1g) at 90°C for 16 hours. The mixture was cooled, adsorbed onto silica and purified by chromatography. Trituration from hexane and filtration gave the title compound (0.20g); δH [$^2H_6$]DMSO 9.78(1H,bs), 9.22(1H,s), 8.57(1H,s), 8.53(1H,s), 7.98(1H,d), 7.83(1H,d), 7.67(2H,d), 7.42(5H,m), 7.09(1H,d), 5.64(2H,s) 2.51 (3H,s); m/z $(M+1)^+$ 409.

Example 86

(4-Benzyloxy-phenyl)-(6-(4-(1,3-dioxolan-2-yl)-3-methyl-3H-imidazol-2-yl)-quinazolin-4-yl)-amine

1-Methyl-5-(1,3-dioxolan-2-yl)-imidazole (0.09g) in dry THF (5ml) under N_2 was cooled to -78°C and treated with n-butyl lithium (0.4ml, 1.6M). After 30 minutes, tributyl tin chloride (0.17ml) was added, the mixture allowed to warm to 20°C and stirred for 1 hour. (4-Benzyloxy-phenyl)-(6-iodoquinazolin-4-yl)-amine (0.191g), catalytic quantities of 1.4-bis-(diphenylphosphino)-butane palladium (II) chloride and silver (I) oxide (0.052g) were added and the mixture heated at reflux for 18 hours. The mixture was absorbed onto silica and chromatographed to give the title compound (0.045g); m/z $(M+1)^+$ 480.

Example 87

2-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-3-methyl-3H-imidazol-4-carbaldehyde

(4-Benzyloxy-phenyl)-(6-(4-(1,3-dioxolan-2-yl)-3-methyl-3H-imidazol-2-yl)-quinazolin-4-yl)-amine (0.06g) was treated with acetone (5ml) and 2N HCl at reflux for 2 hours. The mixture was cooled, partitioned between ethyl acetate and 2N sodium carbonate. The organic phase was dried and concentrated *in vacuo* to give

the title compound which was used directly in any subsequent synthetic step; m/z $(M+1)^+$ 436.

Examples 88 to 95

The following compounds, and their hydrochlorides if appropriate, are prepared by analogous techniques using the corresponding starting materials:
(4-Benzyloxy-phenyl)-(6-(imidazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-[5-(4-methyl-piperazinylmethyl)-1-methylimidazol-2-yl]-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-[5-(*N*,*N*-dimethylaminomethyl)-1-methylimidazol-2-yl]-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-[5-(4-methyl-piperazinylmethyl)-imidazol-2-yl]-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-[5-(*N*,*N*-dimethylaminomethyl)-imidazol-2-yl]-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-[1-(4-methyl-piperazinylmethyl)-imidazol-2-yl]-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-[1-(*N*,*N*-dimethylaminomethyl)-imidazol-2-yl]-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-carboxymethylaminomethyl-furan-2-yl)-quinazolin-4-yl)-amine.

Biological Data

Compounds of the present invention were tested for protein tyrosine kinase inhibitory activity in substrate phosphorylation assays and cell proliferation assays.

The substrate phosphorylation assays use baculovirus expressed, recombinant constructs of the intracellular domains of c-erbB-2 and c-erbB-4 that are constitutively active and EGFr isolated from solubilised A431 cell membranes. The method measures the ability of the isolated enzymes to catalyse the transfer of the γ-phosphate from ATP onto tyrosine residues in a biotinylated synthetic peptide (Biotin-GluGluGluGluTyrPheGluLeuVal). The enzyme is incubated for 30 minutes, at room temperature, with 10mM $MnCl_2$, ATP and peptide at Km concentrations, and test compound (diluted from a 5mM stock in DMSO, final DMSO concentration is 2%) in 40mM HEPES buffer, pH 7.4. The reaction is stopped by the addition of

EDTA (final concentration 0.15mM) and a sample is transferred to a streptavidin-coated 96-well plate. The plate is washed and level of phosphotyrosine on the peptide is determined using a Europium-labelled antiphosphotyrosine antibody and quantified with a time-resolved fluorescence technique. The results are shown in Table 1 as the IC_{50} values in nM.

The cell proliferation assay uses an immortalised human breast epithelial cell line (HB4a) which has been transformed by over-expression of c-erbB-2. Growth of these cells in low serum is dependent upon the c-erbB-2 tyrosine kinase activity. The specificity of the effect of the test compounds on tyrosine kinase dependent growth over general toxicity is assessed by comparison to an HB4a cell line which has been transfected with ras. Cells are plated at 3000/well in 96-well plates in 0.1 ml medium and allowed to attach overnight. test compound is added in 0.1 ml medium, with a final concentration of 0.5% DMSO, and the plates incubated for 4 days at 37°C. The cells are then examined microscopically for evidence of morphological detransformation and cell mass is estimated by staining with methylene blue and measuring the absorbance at 620nm. The results are shown in Table 1 below as the IC_{50} values in nM. Activity against a range of naturally occurring EGFr or c-erbB-2 over-expressing human tumour cell lines (BT474-breast, HN5-head and neck, N87-gastric and Calu3-lung) is assessed with selected compounds by the same methodology. The results are also shown in Table 1 below as the IC_{50} values in nM.

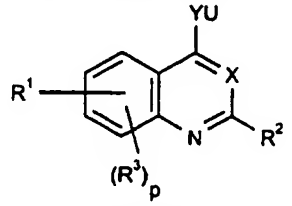
Table 1

Example	Substrate Phosphorylation			Cell Proliferation					
	EGFr	erbB-2	erbB-4	HB4a erbB-2	HB4a ras	BT474	N87	Calu3	HN5
1		40	2500						
2		21	500	1000	8300			4600	26000
3		29	8600	23000	16000				
4		35	6400	50000	50000				
5		20	320	400	19000			780	1400
6	680	110	1000	1600	16000	1900	1800	5800	5200
7		36	1500	1300	12000			4700	5500
8		150	>10000						
9		24	430	550	5700				
10		52	780	1500	7100			2200	2100
11	160	36	660	580	14000	180	480	930	940
12	220	120	1400	840	2500				
13	300	350	2300	450	2200				
14	200	34	1200	680	5000				
15	540	50	2300	2600	3200				
18		45	34	9	>50000	2	180	360	840
19	8	1	240	50	25000	110	380	920	670
20	140	3		6200	>50000				
21	28	9		2300	>50000				
22	8			430	27000	97	600	2200	910
23	32	1		31000	>50000				
24	15	2		17000	>50000				
25	22	15		750	>50000				
26	18	7		650	>50000				

Example	Substrate Phosphorylation			Cell Proliferation					
	EGFr	erbB-2	erbB-4	HB4a erbB-2	HB4a ras	BT474	N87	Calu3	HN5
27	47	10		6500	50000				
28	50	7		5300	>50000		8200		
29	23	3		2500	>50000	770	2400	23000	4400
30	38	6		5400	50000			18000	
31	9			1100	>50000				
38	140	88	520						
40		3	970	>50000	>50000				
41	2	10	1000	610	35000	260	1400	5300	970
42		7		570	20000				
44			1300	1400	31000				
47		490	5000						
48		38	1100	80	9500				
49		33		470	3500				
50		12	100	860	7100				
51		20	5800	38000	21000				
53	13			1800	36000				
54		24	280	140	7400				
55		10	1000	2000	20000				
56		260	>10000	1700	>50000				
57		83		1200	2700				
58		6		8600	28000				
59	11			790	11000				
60	1900			540	50000				
61	810			500	3100				
62	13	100		500	3700				
85		130	9700	2100	2300				

Claims

1. A compound of formula (I):



(I)

or a salt or solvate thereof;

wherein X is N or CH;

Y is a group $W(CH_2)$, $(CH_2)W$, or W, in which W is O, $S(O)_m$ wherein m is 0, 1 or 2, or NR^a wherein R^a is hydrogen or a C_{1-8} alkyl group;

R^1 represents a phenyl group or a 5- or 6-membered heterocyclic ring containing 1 to 4 heteroatoms selected from N, O or $S(O)_m$, wherein m is as defined above, with the provisos that the ring does not contain two adjacent O or $S(O)_m$ atoms and that where the ring contains only N as heteroatom(s) the ring is C-linked to the quinazoline or quinoline ring, R^1 being optionally substituted by one or more R^3 groups;

each R^3 is independently selected from the group comprising amino, hydrogen, halogen, hydroxy, nitro, carboxy, formyl, cyano, trifluoromethyl, trifluoromethoxy, carbamoyl, ureido, guanidino, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-8} cycloalkoxyl, C_{4-8} alkylcycloalkoxy, C_{1-8} alkylcarbonyl, C_{1-8} alkoxycarbonyl, N-C_{1-4} alkylcarbamoyl, N,N-di-[C_{1-4} alkyl]carbamoyl, hydroxyamino, C_{1-4} alkoxyamino, C_{2-4} alkanoyloxyamino, C_{1-4} alkylamino, di[C_{1-4} alkyl]amino, di-[C_{1-4} alkyl]amino-C_{1-4} alkylene-(C_{1-4} alkyl)amino, C_{1-4} alkylamino- C_{1-4} alkylene-(C_{1-4} alkyl)amino, hydroxy-C_{1-4} alkylene-(C_{1-4} alkyl)amino, phenyl, phenoxy, 4-pyridon-1-yl, pyrrolidin-1-yl, imidazol-1-yl, piperidino, morpholino, thiomorpholino, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, piperazin-1-yl, 4-C_{1-4} alkylpiperazin-1-yl, dioxolanyl, C_{1-8} alkylthio, arylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, arylsulphonyl, arylsulphinyl, halogeno-C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, C_{2-4} alkanoyloxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4} alkyl, carboxy-C_{1-4} alkyl, formyl-C_{1-4} alkyl, C_{1-4} alkoxycarbonyl-C_{1-4}-alkyl, carbamoyl-C_{1-4} alkyl, N-C_{1-4} alkylcarbamoyl-C_{1-4}alkyl, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4}alkyl, amino-C_{1-4} alkyl, C_{1-4} alkylamino-C_{1-4}

alkyl, di-[C_{1-4} alkyl]amino-C_{1-4} alkyl, phenyl-C_{1-4} alkyl, 4-pyridon-1-yl-C_{1-4} alkyl, pyrrolidin-1-yl-C_{1-4} alkyl, imidazol-1-yl-C_{1-4} alkyl, piperidino-C_{1-4} alkyl, morpholino-C_{1-4} alkyl, thiomorpholino-C_{1-4} alkyl, thiomorpholino-1-oxide-C_{1-4}alkyl, thiomorpholino-1,1-dioxide-C_{1-4}alkyl, piperazin-1-yl-C_{1-4}alkyl, 4-C_{1-4} alkylpiperazin-1-yl-C_{1-4} alkyl, hydroxy-C_{2-4} alkoxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkoxy-C_{1-4} alkyl, hydroxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkylthio-C_{1-4} alkyl, C_{1-4} alkylsulphinyl-C_{1-4} alkyl, C_{1-4} alkylsulphonyl-C_{1-4} alkyl, hydroxy-C_{2-4} alkylthio-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylthio-C_{1-4} alkyl, phenoxy-C_{1-4} alkyl, anilino-C_{1-4} alkyl, phenylthio-C_{1-4} alkyl, cyano-C_{1-4} alkyl, halogeno-C_{2-4} alkoxy, hydroxy-C_{2-4} alkoxy, C_{2-4} alkanoyloxy-C_{2-4} alkoxy, C_{1-4} alkoxy-C_{2-4} alkoxy, carboxy-C_{1-4} alkoxy, formyl-C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl-C_{1-4} alkoxy, carbamoyl-C_{1-4} alkoxy, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkoxy, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkoxy, amino-C_{2-4} alkoxy, C_{1-4} alkylamino-C_{2-4} alkoxy, di-[C_{1-4} alkyl]amino-C_{2-4} alkoxy, di-[C_{1-4} alkyl-C_{2-4} alkoxy]amino-C_{2-4} alkoxy, C_{2-4} alkanoyloxy, hydroxy-C_{2-4} alkanoyloxy, C_{1-4}alkoxy-C_{2-4} alkanoyloxy, phenyl-C_{1-4} alkoxy, phenoxy-C_{2-4} alkoxy, anilino-C_{2-4} alkoxy, phenylthio-C_{2-4} alkoxy, 4-pyridon-1-yl-C_{2-4} alkoxy, piperidino-C_{2-4} alkoxy, morpholino-C_{2-4} alkoxy, thiomorpholino-C_{2-4} alkoxy, thiomorpholino-1-oxide-C_{2-4} alkoxy, thiomorpholino-1,1-dioxide-C_{2-4} alkoxy, piperazin-1-yl-C_{2-4} alkoxy, 4-C_{1-4} alkylpiperazin-1-yl-C_{2-4} alkoxy, pyrrolidin-1-yl-C_{2-4} alkoxy, imidazol-1-yl-C_{2-4} alkoxy, halogeno-C_{2-4} alkylamino, hydroxy-C_{2-4} alkylamino, C_{2-4} alkanoyloxy-C_{2-4} alkylamino, C_{1-4} alkoxy-C_{2-4} alkylamino, carboxy-C_{1-4} alkylamino, C_{1-4} alkoxycarbonyl-C_{1-4} alkylamino, carbamoyl-C_{1-4} alkylamino, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkylamino, amino-C_{2-4} alkylamino, C_{1-4} alkylamino-C_{2-4} alkylamino, di-[C_{1-4}alkyl]amino-C_{2-4} alkylamino, phenyl-C_{1-4} alkylamino, phenoxy-C_{2-4} alkylamino, anilino-C_{2-4} alkylamino, 4-pyridon-1-yl-C_{2-4} alkylamino, pyrrolidin-1-yl-C_{2-4} alkylamino, imidazol-1-yl-C_{2-4} alkylamino, piperidino-C_{2-4} alkylamino, morpholino-C_{2-4} alkylamino, thiomorpholino-C_{2-4} alkylamino, thiomorpholino-1-oxide-C_{2-4} alkylamino, thiomorpholino-1,1-dioxide-C_{2-4} alkylamino, piperazin-1-yl-C_{2-4}alkylamino, 4-(C_{1-4}alkyl)piperazin-1-yl-C_{2-4}alkylamino, phenylthio-C_{2-4} alkylamino, C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonylamino, C_{1-4} alkylsulphonylamino, C_{1-4} alkylsulphinylamino, benzamido, benzenesulphonamido, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, halogeno-C_{2-4} alkanoylamino, hydroxy-C_{2-4} alkanoylamino, hydroxy-C_{2-4} alkanoyl-(C_{1-4} alkyl)-amino, C_{1-4} alkoxy-C_{2-4} alkanoylamino, carboxy-C_{2-4} alkanoylamino, C_{1-4}

alkoxycarbonyl-C_{2-4} alkanoylamino, carbamoyl-C_{2-4} alkanoylamino, N-C_{1-4} alkylcarbamoyl-C_{2-4} alkanoylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{2-4} alkanoylamino, amino-C_{2-4} alkanoylamino, C_{1-4} alkylamino-C_{2-4} alkanoylamino or di-[C_{1-4} alkyl]amino-C_{2-4} alkanoylamino; and wherein said benzamido or benzenesulphonamido substitutent or any anilino, phenoxy or phenyl group on a R^3 substituent may optionally bear one or two halogeno, C_{1-4} alkyl or C_{1-4} alkoxy substituents; and wherein any substituent containing a heterocyclic ring may optionally bear one or two halogeno, C_{1-4} alkyl or C_{1-4} alkoxy substituents on said ring; and wherein any substituent containing a heterocyclic ring may optionally bear one or two oxo or thioxo substituents on said ring;

or R^3 represents a group selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 wherein

M^1 represents a C_{1-4} alkyl group, wherein optionally a CH_2 group is replaced by a CO group;

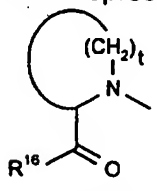
M^2 represents NR^{12} or $CR^{12}R^{13}$, in which R^{12} and R^{13} each independently represent H or C_{1-4} alkyl;

M^3 represents a C_{1-4} alkyl group;

$M^{3'}$ represents a C_{1-4} alkyl group or is absent;

M^4 represents CN, $NR^{12}S(O)_mR^{13}$, $S(O)_mNR^{14}R^{15}$, $CONR^{14}R^{15}$, $S(O)_mR^{13}$ or CO_2R^{13}, in which R^{12}, R^{13} and m are as hereinbefore defined and R^{14} and R^{15} each independently represent H or C_{1-4} alkyl, or R^{14} and R^{15} together with the nitrogen atom to which they are attached represent a 5-or 6-membered ring optionally containing 1 or 2 additional heteroatoms selected from N, O or $S(O)_m$ in which ring any nitrogen atom present may optionally be substituted with a C_{1-4} alkyl group, and which ring may optionally bear one or two oxo or thioxo substituents;

M^5 represents the group $NR^{14}R^{15}$, wherein R^{14} and R^{15} are as defined above, or M^5 represents the group



in which t represents 2 to 4 and R^{16} represents OH, OC_{1-4} alkyl or $NR^{14}R^{15}$; and

M^6 represents a C_{3-6} cycloalkyl group, the group $NR^{14}R^{15}$, wherein R^{14} and R^{15} are as defined above, or a 5- or 6-membered heterocyclic ring system containing 1 to 4 heteroatoms selected from N, O or S;

and p is 0 to 3; or when p is 2 or 3, two adjacent R^3 groups together form an optionally substituted methylenedioxy or ethylenedioxy group;

R^2 is selected from the group comprising hydrogen, halogen, trifluoromethyl, C_{1-4} alkyl and C_{1-4} alkoxy;

U represents phenyl or a 5 to 10-membered mono or bicyclic ring system in which one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and $S(O)_m$, wherein m is 0,1 or 2, and wherein U is substituted by at least one independently selected R^6 group and is optionally substituted by at least one independently selected R^4 group;

each R^4 is independently hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino, di-[C_{1-4} alkyl]amino, C_{1-4} alkylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbamoyl, di-[C_{1-4} alkyl] carbamoyl, carbamyl, C_{1-4} alkoxycarbonyl, cyano, nitro or trifluoromethyl;

each R^6 is independently a group ZR^7 wherein Z is joined to R^7 through a $(CH_2)p$ group in which p is 0, 1 or 2 and Z represents a group $V(CH_2)$, $V(CF_2)$, $(CH_2)V$, $(CF_2)V$, V(CRR'), V(CHR) or V where R and R' are each C_{1-4} alkyl and in which V is a hydrocarbyl group containing 0,1 or 2 carbon atoms, carbonyl, dicarbonyl, CH(OH), CH(CN), sulphonamide, amide, O, $S(O)_m$ or NR^b where R^b is hydrogen or R^b is C_{1-4} alkyl; and R^7 is an optionally substituted C_{3-6} cycloalkyl; or an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety;
or R^6 is a group ZR^7 in which Z is NR^b, and NR^b and R^7 together form an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety.

2. A compound as claimed in claim 1 wherein R^3 is as defined in claim 1 with the exception of wherein any substituent containing a heterocyclic ring bears one or two oxo or thioxo substituents on said ring, and with the exception of C_{1-4} alkylsulphinyl-C_{1-4} alkyl or C_{1-4} alkylsulphonyl-C_{1-4} alkyl; and wherein R^{14} and R^{15} are as defined in claim 1 with the exception of wherein they together with the nitrogen atom to which they are attached represent a 5- or 6-membered ring and said ring bears one or two oxo or

thioxo substituents; save that R^3 may represent 4-pyridon-1-yl, 4-pyridon-1-yl-C_{1-4} alkyl, 4-pyridon-1-yl-C_{2-4} alkoxy, 4-pyridon-1-yl-C_{2-4} alkylamino, 2-oxopyrrolidin-1-yl or 2,5-dioxopyrrolidin-1-yl.

3. A compound as claimed in claim 1 or claim 2 wherein X is N.

4. A compound as claimed in any one of claims 1 to 3 wherein Y is NR^b, $NR^b(CH_2)$, or $(CH_2)NR^b$, preferably Y is NR^b and R^b is preferably hydrogen or methyl.

5. A compound as claimed in any one of claims 1 to 4 wherein R^1 is a 5- or 6-membered heterocyclic ring as defined in claim 1, optionally substituted by one or more R^1 groups selected from the group comprising amino, hydrogen, halogen, hydroxy, hydroxy-C_{1-4} alkyl, formyl, carboxy, cyano, nitro, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, C_{1-8} alkylsulphinyl, C_{1-8} alkylsulphonyl, C_{1-4} alkylamino, C_{1-4} dialkylamino, dioxolanyl or hydroxy-C_{1-4} alkanoyl-(C_{1-4} alkyl)-amino.

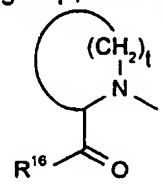
6. A compound as claimed in any one of claims 1 to 4 wherein R^1 is a 5- or 6-membered heterocyclic ring as defined above substituted by one or more R^3 groups selected from the group comprising C_{1-4}alkyl, C_{1-4}alkylamino-C_{1-4}alkyl, di(C_{1-4}alkyl)amino-C_{1-4} alkyl, formyl, carboxy, C_{1-4}alkoxycarbonyl, dioxolanyl or trifluoromethyl.

7. A compound as claimed in any one of claims 1 to 4 wherein R^1 is a 5- or 6-membered heterocyclic ring as defined above substituted by one or more R^3 groups selected from C_{1-4}alkylsulphinyl-C_{1-4}alkyl or C_{1-4}alkylsulphonyl-C_{1-4}alkyl.

8. A compound as claimed in any one of claims 1 to 4 wherein R^1 is a 5- or 6-membered heterocyclic ring as defined in claim 1 substituted with an R^3 group selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined in claim 1 or claim 2; and p = 0.

9. A compound as claimed in any one of claims 1 to 4 or 8 wherein R^1 is a 5- or 6-membered heterocyclic ring as defined above substituted with an R^3 group selected from piperidonyl-methyl, pyrrolidinonyl-methyl or dioxoimidazolidinyl-methyl.

10. A compound as claimed in any one of claims 1 to 4 or 8 wherein M^1 represents CH_2, CO, CH_2CH_2 or CH_2CO; M^2 represents NR^{12} in which R^{12} is as defined in claim 1; M^3 represents CH_2, CH_2CH_2 or propyl; $M^{3'}$ represents CH_2, ethyl, propyl, isopropyl or is absent; M^4 represents SOR^{13}, SO_2R^{13}, $NR^{12}SO_2R^{13}$, $SO_2NR^{14}R^{15}$, CO_2R^{13} or $CONR^{14}R^{15}$ in which R^{12} and R^{13} are defined in claim 1 and R^{14} and R^{15} each independently represent H or C_{1-4} alkyl; M^5 represents a group $NR^{14}R^{15}$ in which R^{14} and R^{15} together with the nitrogen atom to which they are attached represent a 6-membered ring optionally containing an additional heteroatom selected from N or O, in which ring any nitrogen atom present may optionally be substituted with a C_{1-4} alkyl group; or M^5 represents a group



in which t represents 2 or 3 and R^{16} represents OH, NH_2, $N(C_{1-4}$ alkyl$)_2$ or OC_{1-4} alkyl; more preferably R^{16} represents NH_2 or $N(CH_3)_2$; or M^5 represents a group $NR^{14}R^{15}$ in which R^{14} and R^{15} each independently represent hydrogen or C_{1-4} alkyl, more preferably hydrogen, methyl, ethyl or isopropyl; and M^6 represents a group $NR^{14}R^{15}$ in which R^{14} and R^{15} each independently represent C_{1-4} alkyl, more preferably methyl, or R^{14} and R^{15} together with the nitrogen atom to which they are attached represent a 5- or 6-membered ring optionally containing an additional heteroatom selected from N or O, in which ring any nitrogen atom present may optionally be substituted with a C_{1-4} alkyl group, preferably a methyl group; or M^6 represents a 5- or 6-membered heterocyclic ring system containing 1 or 2 heteroatoms selected from N or O.

11. A compound as claimed in any one of claims 1 to 4, 8 or 10 wherein M^2-M^3-M^4 represents an α-amino carboxylic acid or a methyl ester or amide thereof; or M^2-M^3-M^4 represents a β- or γ-amino sulphinic or sulphonic acid or a methyl ester thereof.

12. A compound as claimed in any one of claims 1 to 4, 8, 10 or 11 wherein M^2-M^3-M^4 represents a methylsulphonylethylamino, methylsulphinylethylamino, methylsulphonylethyl(methylamino), methylsulphinylethyl(methylamino), methylsulphonylpropylamino, methylsulphinylpropylamino, methylsulphonamidoethylamino,

aminosulphonylethylamino, methylaminosulphonylethylamino, sarcosinamide, glycine, glycinamide, glycine methyl ester or acetylaminoethylamino group.

13. A compound as claimed in any one of claims 1 to 4, 8 or 10 wherein M^1-M^5 represents a piperazinyl-methyl, methylpiperazinyl-methyl, piperidinyl-methyl, pyridylmethyl, prolinamidomethyl, N,N-dimethylprolinamido-methyl, isopropylacetamido or N-morpholinoacetamido group.

14. A compound as claimed in any one of claims 1 to 4, 8 or 9 wherein M^1-M^5 represents a piperidonyl-methyl, pyrrolidinonyl-methyl or dioxoimidazolidinyl-methyl group.

15. A compound as claimed in any one of claims 1 to 4, 8 or 10 wherein M^2-$M^{3'}$-M^6 represents a pyridylamino, cyclopropylamino, N-(piperidin-4-yl)-N-methylamino, N,N-dimethylaminoprop-2-ylamino, N-(2-dimethylaminoethyl)-N-ethylamino or tetrahydrofuranomethylamino group, preferably a pyridylamino group.

16. A compound as claimed in any one of claims 1 to 15 wherein R^1 is selected from the group comprising furan, dihydrofuran, thiophene, imidazole, tetrazole, triazole, pyridine, pyrrole, pyrimidine, isoxazole or oxadiazole.

17. A compound as claimed in any one of claims 1 or 3 to 15 wherein R^1 is an oxadiazolidinone ring.

18. A compound as claimed in claim 16 wherein R^1 is selected from the group comprising furan, imidazole, oxadiazole (particularly 1,3,4-oxadiazole and 1,2,4-oxadiazole) and triazole (particularly 1,2,3-triazole and 1,3,4-triazole).

19. A compound as claimed in any one of claims 1 to 18 wherein R^6 is benzyl, fluorobenzyl, difluorobenzyl, benzyloxy, fluorobenzyloxy, pyridylmethyl, phenyl, benzenesulphonyl, phenoxy or fluorophenoxy.

20. A compound as claimed in claim any one of claims 1 to 19 wherein U represents an phenyl, indolyl, isoindolyl, indolinyl, isoindolinyl, 1H-indazolyl, 2,3-dihydro-1H-indazolyl, 1H-benzimidazolyl, 2,3-dihydro-1H-benzimidazolyl or 1H-benzotriazolyl group.

21. A compound as claimed in claim 20 wherein U represents a phenyl or 1H-indazolyl group.

22. A compound as claimed in any one of claims 1 to 21 wherein the optional substituents for the carbocyclic or heterocyclic moiety and also for other optionally substituted groups include hydroxy, halogen, trifluoromethyl, trifluoromethoxy, nitro, amino, cyano, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkyl carbonyl, carboxylate and C_{1-4} alkoxy carboxyl.

23. A compound of formula (I) or a salt or solvate thereof as claimed in any one of claims 1 to 6 wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; R^1 represents furan, thiophene, pyrrole, pyridine, pyrimidine, pyrazine, imidazole, oxazole, isoxazole, oxadiazole, tetrazole, triazole, dioxolane or a partially or fully hydrogenated derivative of any of these groups, optionally substituted by one or more R^3 groups selected from halo, trifluoromethyl, C_{1-4} alkyl, carboxy, C_{1-4}-alkoxycarbonyl, formyl, hydroxy-C_{1-4} alkyl, 1,3-dioxolan-2-yl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy-C_{1-4}alkanoyl-(C_{1-4}alkyl)-amino, C_{1-4} alkylamino-C_{1-4} alkyl or di(C_{1-4} alkyl)amino-C_{1-4} alkyl; p is 0; R^2 represents hydrogen; R^4 represents hydrogen, halo or methyl; U represents phenyl, indolyl, benzimidazolyl or indazolyl, more preferably phenyl or indazolyl; and R^6 represents phenyl, benzyl, α-methylbenzyl, fluorobenzyl, difluorobenzyl, pyridylmethyl, benzenesulphonyl, phenoxy, fluorophenoxy, benzyloxy or fluorobenzyloxy.

24. A compound of formula (I) or a salt or solvate thereof as claimed in any one of claims 1 to 4, 8 to 13 or 15 wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; R^1 represents furan, thiophene, pyrrole, pyridine, pyrimidine, pyrazine, imidazole, oxazole, isoxazole, oxadiazole, tetrazole, triazole, dioxolane or a partially or fully hydrogenated derivative of any of these groups, optionally substituted with an R^3 group selected from methylsulphonylethylaminomethyl, methylsulphonylethylamino-carbonyl, methylsulphinylethylamino-methyl, methylsulphinylethylamino-carbonyl, methylsulphonylpropylamino-methyl, methylsulphinylpropylamino-methyl, methylsulphonylpropyamino-carbonyl, methylsulphinylpropylamino-carbonyl, methylsulphonylethyl-(methylamino)-methyl, methylsulphonylethyl-(methylamino)-carbonyl, methylsulphinylethyl-(methylamino)-methyl, methylsulphinylethyl-(methylamino)-carbonyl, methylsulphonylpropyl-

(methylamino)-methyl, methylsulphinylpropyl-(methylamino)-methyl, methylsulphonylpropyl-(methylamino)-carbonyl, methylsulphinylpropyl-(methylamino)-carbonyl, methylsulphonamidoethylamino-methyl, methylsulphonamidopropylamino-methyl, aminosulphonylethylaminomethyl, methylaminosulphonylethylaminomethyl, sarcosinamidomethyl, glycinylmethyl, glycinamidomethyl, glycinylmethyl methyl ester, acetylaminoethylaminomethyl, piperazinylmethyl, methylpiperazinylmethyl, piperidinylmethyl, pyridylmethyl, N-(prolinamido)methyl, (N,N-dimethyl-prolinamido)methyl, pyridylaminomethyl, cyclopropylaminomethyl, N-(piperidin-4-yl)-N-methylaminomethyl, N,N-dimethylaminoprop-2-ylaminomethyl, N-(2-dimethylaminoethyl)-N-ethylaminomethyl, isopropylacetamido, N-morpholinylacetamido or tetrahydrofuranomethylaminomethyl and optionally further substituted by one or more C_{1-4} alkyl groups; p is 0; R^2 represents hydrogen; R^4 represents hydrogen, halo or methyl; U represents phenyl, indolyl, benzimidazolyl or indazolyl, more preferably phenyl or indazolyl; and R^6 represents phenyl, benzyl, α-methylbenzyl, fluorobenzyl, difluorobenzyl, pyridylmethyl, benzenesulphonyl, phenoxy, fluorophenoxy, benzyloxy or fluorobenzyloxy.

25. A compound of formula (I) or a salt or solvate thereof as claimed in claim 23 or claim 24 wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; R^1 represents a furan, dihydrofuran, thiophene, pyridine, pyrrole, pyrimidine, isoxazole, triazole, tetrazole, imidazole or oxadiazole ring, preferably furan, imidazole, oxadiazole and triazole, substituted with an R^3 group selected from C_{1-4}alkyl, C_{1-4}alkylamino-C_{1-4}alkyl, di(C_{1-4}alkyl)amino-C_{1-4} alkyl, formyl, carboxy, C_{1-4}alkoxycarbonyl, dioxolanyl, trifluoromethyl, methylsulphonylethylaminomethyl, methylsulphonylethylamino-carbonyl, methylsulphonylethyl(methylamino)-methyl, methylsulphonamidoethylamino-methyl, aminosulphonylethylamino-methyl, methylaminosulphonylethylamino-methyl, N,N-dimethylaminoprop-2-ylaminomethyl, N-(2-dimethylaminoethyl)-N-ethylaminomethyl, pyridylaminomethyl, tetrahydrofuranomethylaminomethyl, piperazinylmethyl, methylpiperazinylmethyl, piperidinylmethyl, pyridylmethyl, N-(prolinamido)methyl or (N,N-dimethyl-prolinamido)methyl; p is 0; R^2 represents hydrogen; R^4 represents hydrogen or halo; U represents phenyl or indazolyl; and R^6 represents benzyl, fluorobenzyl, difluorobenzyl, pyridylmethyl, benzenesulphonyl, phenoxy, benzyloxy or fluorobenzyloxy.

26. A comound as claimed in claim 1 or claim 2 selected from:
(4-Benzyloxy-phenyl)-(6-furan-2-yl-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(thiophen-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(pyridin-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(pyrimidin-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(3-methyl-3H-imidazol-4-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(2,3-dihydrofuran-5-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(3-methyl-1,2,3-triazol-4-yl)-quinazolin-4-yl)-amine;
5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde;
(4-Benzyloxy-phenyl)-(6-(5-(4-methylpiperazin-1-ylmethyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(S)-1-(5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-pyrrolidine-2-carboxylic acid amide;
N2-(5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-N1,N1-dimethyl-propane-1,2-diamine;
N-(5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-N-ethyl-N',N'-dimethyl-ethane-1,2-diamine;
(4-Benzyloxy-phenyl)-(6-(5-(pyridin-3-ylaminomethyl)-furan-2-yl)quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-(((tetrahydro-furan-2-ylrnethyl)-amino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-(1,3)-dioxolan-2-yl-furan-2-yl)-quinazolin-4-yl)-amine;
5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-furan-2-carbaldehyde;
(S)-1-(5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-pyrrolidine-2-carboxylic acid amide;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)quinazolin-4-yl)-amine;
(1-(2-Fluorobenzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;

(1-(3-Fluorobenzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-Pyridin-2-ylmethyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-(2,3-Difluorobenzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)quinazolin-4-yl)-amine;
(3-Chloro-4-(2-fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(3-Chloro-4-(3-fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(2-Fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolinyl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-(3,5-Difluoro-benzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine
(4-(4-Fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(2-Fluoro-benzyloxy)-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(4-Fluoro-benzyloxy)-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Pyridin-3-ylmethoxy)-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(3-methyl-3H-imidazol-4-yl)-quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(1-methyl-1H-imidazol-2-yl)quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(1H-tetrazol-5-yl)-quinazolin-4-yl)-amine;

(1-Benzyl-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl0-amine;

(1-Benzyl-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-triazol-2-yl)-quinazolin-4-yl)-amine;

(S)-1-(2-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-3-methyl-3H-imidazol-4-ylmethyl)-pyrrolidine-2-carboxylic acid amide;

(1-Benzyl-1H-indazol-5-yl)-(6-(5-methanesulphonylmethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(1-methylpyridinium-2-yl)quinazolin-4-yl)-amine; chloride;

(4-Benzyloxy-phenyl)-(6-(2,3-dimethyl-3H-imidazol-4-yl)-quinazolin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(-6-(3-methylisoxazol-5-yl)-quinazolin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(5-(((2-methanesulphonyl-ethyl)-methyl-amino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;

N-(2-((5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-amino)-ethyl)-methanesulphonamide;

2-((5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-amino)-ethanesulphonic acid amide;

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carboxylic acid methyl ester;

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carboxylic acid;

5-[4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl]-furan-2-carboxylic acid (2-methanesulphonyl-ethyl)-amide;

2-((5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-amino)-ethanesulphonic acid methylamide;

(1-Benzyl-1H-indazol-5-yl)-(6-(3-methyl-1,2,4-oxadiazol-5-yl)-quinazolin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(5-methyl-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(5-(2-dimethylamino-ethyl)-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(5-(dimethylaminomethyl)-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine;

(1-Benzyl-1H-indazol-5-yl)-(6-(5-(((2-methanesulphonyl-ethyl)-amino)-methyl)-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine;

(1-Benzyl-1H-indazol-5-yl)-(6-(5-methanesulphonylmethyl-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine;

(1-Benzyl-1H-indazol-5-yl)-(6-(5-methyl-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl0-amine;

(1-Benzyl-1H-indazol-5-yl)-6-(5-(pyridin-3-ylmethyl)-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine;

(1-Benzyl-1H-indazol-5-yl)-(6-(1-methylpyrrol-2-yl)-quinazolin-4-yl)-amine;

5-(4-(1-Benzyl-1H-indazol-5-yl)-quinazolin-6-yl)-1-methyl-pyrrole-2-carbaldehyde;

1-(3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-1,2,4-oxadiazol-5-ylmethyl)-piperidin-4-one;

1-(3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-1,2,4-oxadiazol-5-ylmethyl)-pyrrolidin-2-one;

1-(3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-1,2,4-oxadiazol-5-ylmethyl)-imidazolidin-2,5-dione;

3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-4H-1,2,4-oxadiazolidin-3-one;

(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesuphonyl-ethyl-amino)-methyl)-1-methyl-pyrrol-2-yl)-quinazolin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(1-(3-N,N-dimethylaminopropyl)-imidazol-5-yl)-quinazolin-4-yl)-amine;

(1-Benzyl-1H-indazolyl)-(6-(1-(3-N,N-dimethylaminopropyl)-imidazol-5-yl)-quinazolin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(1-(3-N,N-dimethylaminopropyl)-imidazol-2-yl)-quinazolin-4-yl)-amine;

(1-Benzyl-1H-indazolyl)-(6-(1-(3-N,N-dimethylaminopropyl)-imidazol-5-yl)-quinazolin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;

(1-(2-Fluoro-benzyl)-1H-indazol-5-yl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;

(1-(3-Fluoro-benzyl)-1H-indazol-5-yl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;

(1-(4-Fluoro-benzyl)-1H-indazol-5-yl)-(6-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-quinazolin-4-yl)-amine;

(1-Benzyl-1H-indazol-5-yl)-(7-(5-methyl-[1,3,4]oxadiazol-2-yl)-quinazolin-4-yl)-amine;

(1-Benzyl-1H-indazol-5-yl)-(7-(3-methyl-3H-imidazol-4-yl)quinazolin-4-yl)-amine;

(1-Benzyl-1H-indazol-5-yl)-[7-(furan-2-yl)-quinazolin-4-yl]-amine;

(1-Benzyl-1H-indazol-5-yl)-[7-(5-(1,3-dioxolan-2-yl)-furan-2-yl)quinazolin-4-yl] amine;
5-[4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-7-yl]-furan-2-carbaldehyde;
(1-Benzyl-1H-indazol-5-yl)-[7-{5-[(2-methanesulphonyl-ethylamino)-methyl]-furan-2-yl}-quinazolin-4-yl]-amine;
(S)-1-{5-[4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-7-yl]-furan-2-yl-methyl}-pyrrolidine-2-carboxylic acid amide;
(4-Benzyloxy-phenyl)-(6-(3-methyl-[1,2]oxazol-4-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(4-(1,3-dioxolan-2-yl)-3-methyl-3H-imidazol-2-yl)-quinazolin-4-yl)-amine;
2-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-3-methyl-3H-imidazol-4-carbaldehyde;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

27. A compound as claimed in claim 26 selected from:
(4-Benzyloxy-phenyl)-(6-furan-2-yl-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(3-methyl-3H-imidazol-4-yl)-quinazolin-4-yl)-amine;
(4-(4-Fluoro-benzyloxy)-phenyl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)quinazolin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-triazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-methyl-1,2,4-oxadiazol-3-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-(4-methylpiperazin-1-ylmethyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(S)-1-(5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-pyrrolidine-2-carboxylic acid amide;
(S)-1-(5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-pyrrolidine-2-carboxylic acid amide;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-(((2-methanesulphonyl-ethyl)-methyl-amino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
N-(2-((5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-ylmethyl)-amino)-ethyl)-methanesulphonamide;

1-(3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-1,2,4-oxadiazol-5-ylmethyl)-piperidin-4-one;
1-(3-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-1,2,4-oxadiazol-5-ylmethyl)-pyrrolidin-2-one;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

28. A pharmaceutical formulation comprising at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

29. A pharmaceutical formulation as claimed in claim 28 in unit dosage form and containing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in an amount of from 70 to 700mg.

30. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy.

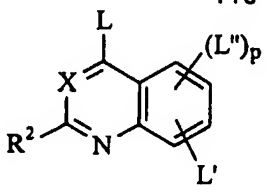
31. The use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, in the treatment of disorders mediated by aberrant protein tyrosine kinase activity.

32. The use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, in the treatment of cancer and malignant tumours.

33. The use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, in the treatment of psoriasis.

34. A method of treatment of a human or animal subject suffering from a disorder mediated by aberrant protein tyrosine kinase activity which comprises administering to the human or animal subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

35. A process for the preparation of a compound of formula (I) as defined in claim 1 or claim 2 which comprises the steps:
(a) the reaction of a compound of formula (II)

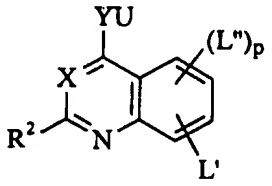


(II)

wherein X, p and R^2 are as defined in claim 1 and L, L' and L" are suitable leaving groups, with a compound of formula (III)

UYH (III)

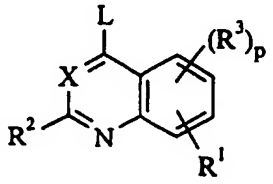
wherein U and Y are as defined in claim 1, to prepare a compound of formula (IV)



(IV)

and subsequently (b) reaction with an appropriate reagent to substitute the group R^1 onto the phenyl ring by replacement of the leaving group L'; and (c) where p is other than 0, reaction with appropriate reagent(s) to substitute the group(s) R^3 onto the phenyl ring by replacement of the leaving group(s) L"; and, if desired, (d) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

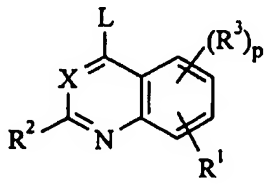
36. A process for the preparation of a compound of formula (I) as defined in claim 1 or claim 2 in which the compound of formula (II) as defined in claim 35 is reacted with the appropriate to substitute the groups R^1 and R^3 onto the phenyl ring by replacement of the respective leaving groups and then the product thereby obtained of formula (V)



(V)

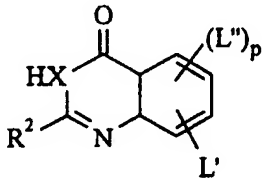
is reacted with the compound of formula (III) as defined in claim 35, followed, if desired, by conversion of the compound of formula (I) thereby obtained into another compound of formula (I).

37. A process as claimed in claim 36 wherein the compound of formula (V)



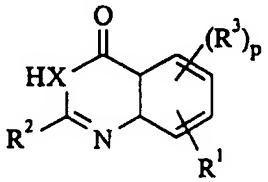
(V)

is prepared by the reaction of a compound of formula (VI)



(VI)

with appropriate reagents to substitute the group(s) R^3 and the group R^1 onto the phenyl ring to prepare a compound of formula (VII)



(VII)

and subsequent reaction to incorporate the leaving group L.

38. A process for the preparation of a compound of formula (I) as defined in claim 1 or claim 2 which comprises the steps:
(a) reacting a compound of formula (IV) as defined in claim 35 with appropriate reagent(s) to prepare a compound wherein either the group L' or the group(s) L'' (when p is other than 0) is(are) replaced with an appropriately functionalised group Z;
and (b) subsequently converting the group Z into the group R^1 where L' has been replaced or into the group R^3 where L'' has been replaced by means of appropriate reagent(s); (c) reacting with appropriate reagents to substitute the other of R^3 and R^1 onto the phenyl ring by replacement of the remaining

leaving group L" and L' respectively, if present; and, if desired, (d) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

39. A process for the preparation of a compound of formula (I) as defined in claim 1 or claim 2 which comprises the steps:
(a) reacting a compound of formula (II) as defined in claim 35 with appropriate reagent(s) to prepare a compound wherein either the group L' or the group(s) L" (when p is other than 0) is(are) replaced with an appropriately functionalised group Z;
and (b) subsequently converting the group Z into the group R^3 where L' has been replaced or into the group R^1 where L" has been replaced by means of appropriate reagent(s); (c) reacting with appropriate reagents to substitute the other of R^1 and R^3 onto the phenyl ring by replacement of the remaining leaving group L" and L' respectively, if present; (d) the product thereby obtained is reacted with the compound of formula (III) as defined in claim 35; and, if desired, (e) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

40. Compounds of formulae (II), (III), (IV), (V), (VI) and (VII) as defined in any one of claims 35 to 37 wherein X, Y, U, R^1, R^2 and p are as defined in any one of claims 1 to 25.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/03672

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D405/04 A61K31/505 C07D409/04 C07D401/04 C07D403/04
C07D405/14 C07D401/14 C07D413/04 C07D413/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 97 30034 A (ZENECA LTD) 21 August 1997 see claim 1 ---	1-40
P,X	WO 97 03069 A (GLAXO GROUP LTD ;COCKERILL GEORGE STUART (GB); CARTER MALCOLM CLIV) 30 January 1997 see claim 1 ---	1-40
X	WO 96 16960 A (ZENECA LTD ;BARKER ANDREW JOHN (GB)) 6 June 1996 cited in the application see claim 1 ---	1-40
X	WO 96 15118 A (ZENECA LTD ;BROWN DEARG SUTHERLAND (GB); MORRIS JEFFREY JAMES (GB)) 23 May 1996 see claim 1 ---	1-40

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search
23 October 1997

Date of mailing of the international search report
19. 11. 97

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Authorized officer
Gettins, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte...tional Application No
PCT/EP 97/03672

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 09294 A (WELLCOME FOUND ;HUDSON ALAN THOMAS (GB); VILE SADIE (GB); BARRACLO) 28 March 1996 cited in the application see claim 1	1-40
Y	WO 95 15758 A (RHONE POULENC RORER PHARMA ;MYERS MICHAEL R (US); SPADA ALFRED P () 15 June 1995 cited in the application see claim 1	1-40
Y	EP 0 566 226 A (ZENECA LTD) 20 October 1993 see claim 1	1-40
A	BRIDGES ET AL: "Tyrosine Kinase Inhibitors" J.MED.CHEM, vol. 39, no. 1, 5 January 1996, pages 267-276, XP000574749 see table 1	1-40
A	REWCASTLE ET AL: "Tyrosine Kinase Inhibitors" J.MED.CHEM., vol. 38, no. 18, 1995, pages 3482-3487, XP002044372 see table 1	1-40

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 97/03672

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

International Application No. PCT/EP 97 03672

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of ----------the following reasons:

Claims Nos.: 37

because they relate to subject matter not required to be searched by this Authority, namely:

Scope unclear

Claims Nos.: 37

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 37 claims the intermediates (II)-(VII) and is only partially searchable. It is pointed out that in its present form claim 37 is also not acceptable because it has been used to claim 6 structurally distinct different set of intermediates. Claim 37 should be divided into 6 claims; one for each set. The intermediates (VII) can be fully searched, but the intermediates (II), (IV)-(VI) cannot be fully searched since their precise scope is not clear due to their containing the definitions "leaving groups" i.e. a structural feature has been defined by a result to be achieved. Only the actual examples and the preffered embodiments listed on page 36 can be searched. Compounds (III) of formula UYH cannot be fully searched. The U component can vary markedly as can the Y component. The very large potential number of combinations is not limited by the fuesed ring found in (I). A complete search is therefore impossibe. (III) has only be searched in so far as it is actually exemplified.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. ..ional Application No
PCT/EP 97/03672

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